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THE EFFECT OF SPECIFIC AGENTS EXTRACTED FROM SOIL MICROÖRGANISMS UPON EXPERIMENTAL BACTERIAL INFECTIONS *

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ORGANIC matter does not accumulate in nature; it rapidly becomes the prey of countless species of microörganisms which break it down, stepwise, to carbon dioxide, water, ammonia, and mineral salts. It is known moreover that, under natural conditions, each one of these microbial species is adapted to the performance of a limited, well-defined biochemical task. It seems certain, therefore, that one can find in nature microörganisms selectively adapted to the decomposition of almost every conceivable type of organic compound.[9]

Like all living cells, microörganisms carry out their biochemical function through the agency of enzymes and other catalysts. In many cases these catalysts can be extracted in an active form from the microbial cells which produce them, and they are often found to exhibit a remarkable specificity with reference to the type of reaction which they can bring about. Because of their cellular origin, microbial catalysts are able to operate under physiological conditions (pH, temperature, etc.) and this property together with their specificity, renders them ideal reagents for the analysis of biological problems. It is apparent, therefore, that one can select from microbial life a great variety of specific, physiological reagents, which should find many applications in the problems of medicine.[9, 10]

During the past few years, this point of view has found its application in the isolation from soil of new bacterial species, which produce specific catalysts selectively adapted to the study of some biochemical and immunological problems.[9, 10, 14, 15, 25] The present report deals with two types of reagents which were extracted from various species of soil bacteria and which, by entirely different mechanisms, protect experimental animals against certain bacterial infections.

* Read at the Cleveland meeting of the American College of Physicians, April 4, 1940.
From The Hospital of The Rockefeller Institute for Medical Research.

Bacterial Enzymes Which Decompose the Capsular Polysaccharides of Virulent Pneumococci. It is well known that the capsular polysaccharides of encapsulated pneumococci determine the serological specificity and condition the virulence of these organisms. The specific antibodies present in the sera of animals immunized with encapsulated pneumococci of the different types, afford protection against pneumococcus infections because of their ability to react with the polysaccharides which constitute the bacterial capsules.[1, 2, 20] It will be shown in the following discussion that enzymes capable of decomposing the capsular substances of pneumococci can also protect experimental animals against infection with these organisms.

As far as is known, the capsular polysaccharides of pneumococci are not decomposed by enzymes of animal or plant origin, nor are they attacked by common species of bacteria, actinomyces or molds. It was possible, however, to isolate from soil a new bacterial species, a sporulating bacillus, which hydrolyzes the specific polysaccharide of Type III pneumococcus.[11] From cultures of this soil bacillus, one can extract a soluble enzyme which hydrolyzes this specific carbohydrate[5, 11, 12] and which robs it at the same time of its serological activity; the enzyme is extraordinarily specific in its action against the polysaccharide of pneumococci of Type III and in particular has been found inactive against all the other bacterial polysaccharides so far tested.[4]

The addition of active enzyme to nutrient media does not inhibit the growth or cause the lysis of pneumococci; however, pneumococci of Type III, when cultivated in media containing the specific enzyme, appear deprived of their capsules and fail to agglutinate in specific antiserum of the homologous type. That the *function* of elaborating the type-specific substance is not destroyed by the enzyme, however, is shown by the fact that pneumococci so treated continue to produce the capsular polysaccharide, when transferred to a medium devoid of the active hydrolyzing agent. These two facts, namely, the decomposition of the isolated specific carbohydrate and the destruction of the capsule, without interference with the essential metabolic functions of the pneumococcus cells, indicate that the active principle is directed against this single, specific substance—the capsular polysaccharide—and not against the cell as a whole.[11]

Enzymes capable of attacking the capsular polysaccharides of other pneumococcus types have now been obtained from different strains of soil bacteria.[25, 26, 27, 28, 29] Several of these enzymes exhibit a remarkable specificity and can even differentiate between polysaccharides which give cross-reactions in immune antisera. For instance, the polysaccharide of gum acacia which reacts in Type III pneumococcus antiserum is not affected by the enzyme which hydrolyzes the Type III polysaccharide.[11] Even more striking is the difference between the two enzymes attacking the polysaccharides of Type III and Type VIII pneumococcus. Both these substances are composed of glucose and glucuronic acid in different ratios, and because of this chemical

relationship, they exhibit a certain amount of cross reaction in immune sera.[17, 21] On the contrary, the bacterial enzymes developed against each one of the polysaccharides fail to attack the other [30]; in other words, the enzymes are even more specific than are the antibodies obtained by immunization of experimental animals with the capsular antigens of pneumococci.

Not only are the bacterial polysaccharidases capable of decomposing the capsular substances in vitro, but they also exhibit the same activity in vivo.[3] In fact, they can protect experimental animals against infection with virulent pneumococci. In view of the specificity which the enzymes exhibit in vitro, it was to be expected that the protection induced in experimental animals would exhibit a specificity determined by the chemical nature of the polysaccharide of the particular pneumococcus type used for infection.[3, 18, 19] It is shown in table 1 for instance, that the enzyme which decomposes the Type

TABLE I

Specificity of the Protective Action of Type III Enzyme
(Reprinted from the Journal of Experimental Medicine)

Infecting dose of Pneumococcus	Enzyme (Lot 4-α) 0.5 c.c.			No enzyme		
	Pneumococcus Type I	Pneumococcus Type II	Pneumococcus Type III	Virulence controls		
				Type I	Type II	Type III
c.c.						
0.1	—	—	S	—	—	—
0.01	—	—	S	—	—	—
0.001	—	—	S	—	—	—
0.0001	D20	D34	S	—	—	—
0.00001	D24	D34	S	D22	D36	D34
0.000001	D34	D34	S	D34	D36	D34
0.0000001	—	—	—	D34	D20	D72

S = survived.
D = Death of animal; the numeral indicates the number of hours before death, or the time at which the animal was found dead.
— = Not done.

III capsular substance can protect mice against infection with 1,000,000 fatal doses of pneumococci of this type, but is entirely ineffective against pneumococci of Types I and II. The same enzyme exhibits also a curative effect on the dermal infection of rabbits caused by Type III pneumococci.[18, 19] Following the injection of the enzyme in suitable amounts into infected rabbits, the blood stream becomes free of bacteria, the focal area of infection becomes sterilized and the disease process ceases. The enzyme also exerts a favorable influence upon experimental pneumonia produced in monkeys of the *M. cynomologos* species with Type III pneumococci. Treatment was followed by cessation of spread of the pneumonic lesion, sterilization of the blood, and early recovery except in animals in which the severity of the dis-

ease was extreme. Whereas in the untreated animals a high incidence of empyema and pericarditis was observed, suppurative complications were apparently prevented by adequate enzyme therapy.[16]

The mechanism of the protection so induced has been revealed by a study of the peritoneal exudate of mice during the course of infection with Type III pneumococci.[3] As could be expected, the peritoneal exudate of the untreated mice showed numerous encapsulated pneumococci free in the fluid and the number of encapsulated bacteria increased as the infection progressed. In contrast to this, the pneumococci in the enzyme-treated animals were already found to be devoid of capsules two hours after treatment. At the end of four hours, the treated animals showed only a few decapsulated cells outside of the leukocytes although many bacteria were present in the phagocytic cells. It is obvious, therefore, that the protective action of the enzyme lies in its capacity to decompose the capsular substance of the infectious agent, and thus to render the latter susceptible to phagocytosis (figures 1, 2, 3, 4).

An understanding of this mechanism makes clear the therapeutic limitations of the enzyme. This reagent only initiates a process which has to be completed by the phagocytic cells of the infected host. When, however, the disease process is of extreme severity and the entire cellular mechanism of the body is markedly depressed, the animal may no longer possess the capacity to dispose of the organisms rendered vulnerable by the specific action of the enzyme.

A Selective Bactericidal Agent Extracted from Cultures of a Sporulating Bacillus. As stated in the introduction, one can discover in nature microorganisms capable of decomposing almost every conceivable type of organic substance. It appeared possible that there also exist microörganisms capable of attacking not only soluble, isolated compounds, but even the intact liv-

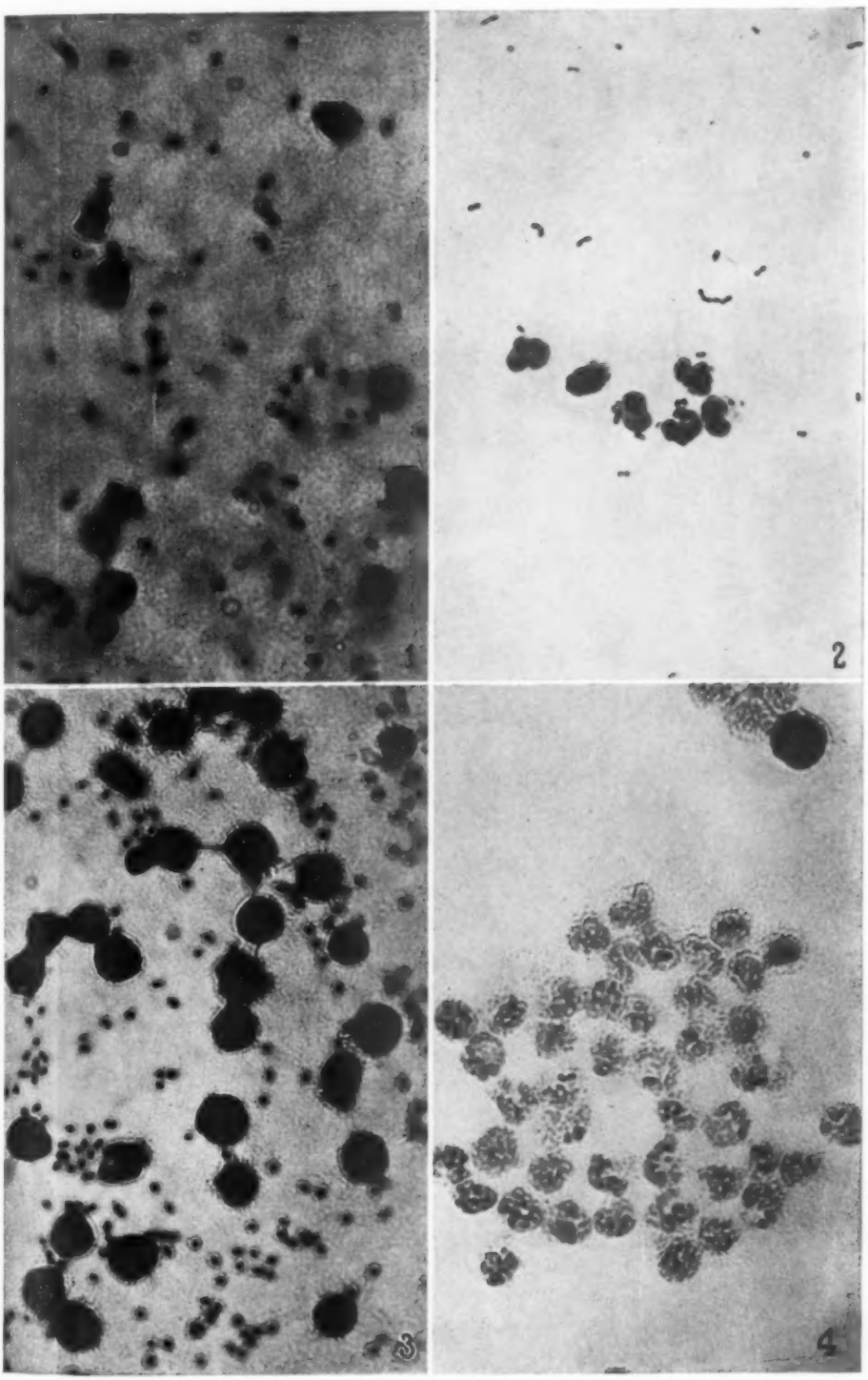
FIG. 1. Photomicrograph of a stained preparation of the peritoneal exudate of a mouse 2 hours after the intraperitoneal injection of 0.01 c.c. of virulent culture of Type III pneumococcus. The bacteria show well-defined capsules and no evidence of phagocytosis is seen. Many polymorphonuclear and a moderate number of mononuclear leukocytes are present. Gram stain. × 1000. Courtesy of the Journal of Experimental Medicine.

FIG. 2. Photomicrograph of a corresponding preparation of the exudate of a mouse 2 hours after receiving the same amount of culture together with 0.5 c.c. of a preparation of the specific enzyme. The bacteria are devoid of capsules. Polymorphonuclear leukocytes predominate and phagocytosis is evident. Gram stain. × 1000. Courtesy of the Journal of Experimental Medicine.

FIG. 3. Photomicrograph of a stained film of the peritoneal exudate of a mouse 4 hours after injection with 0.01 c.c. of culture alone. The bacteria are increased in number, encapsulated, and extracellular. The cellular elements are polymorphonuclear and mononuclear leukocytes in about equal numbers. Gram stain. × 1000. Courtesy of the Journal of Experimental Medicine.

FIG. 4. Photomicrograph of a corresponding preparation of the exudate of a mouse 4 hours after receiving the same amount of culture together with 0.5 c.c. of a preparation of the specific enzyme. Marked phagocytosis has occurred and only an occasional organism is seen outside the accumulated leukocytes, nearly all of which are of the polymorphonuclear type. Gram stain. × 1000. Courtesy of the Journal of Experimental Medicine.

(Differences in the density of the backgrounds of figures 1–4 are due to the use of color screens in the photographic reproductions. This technic, however, alters none of the essential details observed in the original microscopic preparations.)



FIGS. 1–4

ing cells of other, unrelated microbial species. Specifically, it was attempted to discover soil microörganisms that could attack the living cells of Gram positive cocci. To achieve this end, suspensions of living pneumococci, streptococci and staphylococci were added to a soil mixture which was maintained at neutral reactions under aerobic conditions, in the hope that there would develop in the soil sample a microbial flora antagonistic to the Gram positive cocci. In fact, it was possible to isolate from this soil preparation an aerobic sporulating bacillus, belonging to the vast group typified by *Bacillus mesentericus,* which produces a soluble principle extremely toxic for Gram positive bacteria.[6]

This bactericidal principle is abundantly produced when the soil bacillus is grown under strict aerobic conditions in certain peptone media; it can be obtained in solution in an active form free of the bacterial cells which produce it. In fact, several different substances, which all have in common a marked selective bactericidal effect for Gram positive bacteria, have been obtained in solution from peptone cultures of the same bacillus; it is likely that these different active substances are breakdown products of a common mother substance, and result from the manipulations inherent to the technics of extraction and purification. In any case, these different substances exhibit different physiological activities, and their nature and properties will be considered separately.

The bactericidal agent is very soluble in alcohol, acetone, and dioxane. It can be obtained in solution by extraction of an acid precipitate (pH 4.7) of the culture of the soil bacillus with any one of these organic solvents. The bactericidal material is on the contrary very insoluble in ether and in aqueous media; it can be precipitated from the alcoholic solution by diluting the latter with large volumes of aqueous saline. The precipitate can be desiccated and carries the bactericidal activity of the original culture.[13]

The material thus obtained is free of protein. It can be further purified by differential fractionation in alcohol-ether mixtures. The bactericidal material can thus be collected in two fractions: (1) material insoluble in a mixture of one volume of alcohol and fifteen volumes of ether, and (2) material soluble in the same mixture but insoluble in pure ether.[22, 23]

From fraction (1) there were isolated by crystallization from alcohol two crystalline acidic substances which have been designated graminic acid and gramidinic acid. Acetone solutions of fraction (2) have yielded a crystalline neutral substance which has been named gramicidin. The complete chemical structure of these substances is as yet unknown. It can be stated at this time, however, that all of them consist largely of amino acids, probably combined as polypeptides. Gramicidin, which has been most carefully studied, has a molecular weight of about 1400 and contains 2–3 tryptophane residues per molecule; a large percentage of the other amino acids appear to be present in the *d*-(so-called unnatural) form; gramicidin also contains an aliphatic fatty acid, but neither free acid nor basic group (figures 5, 6).

As stated above, graminic acid, gramidinic acid and gramicidin are endowed with bactericidal activity; 0.005 to 0.01 mg. of these substances is sufficient to kill in vitro 10^9 pneumococci, or group A streptococci, in two

FIG. 5. Photomicrograph of crystals of gramicidin. × 225.
(Reproduced by courtesy of Dr. R. D. Hotchkiss)

hours at 37° C. Still smaller amounts inhibit the growth of Gram positive bacteria in nutrient broth. This is particularly striking in the case of pneumococci which fail to grow in broth containing a dilution of 1 : 1,000,000,000 of the active substance.[13]

Not only pneumococci and streptococci but also other Gram positive organisms such as staphylococci, diphtheria and diphtheroid bacilli, and sporulating bacilli are rapidly killed by the same bactericidal principle, although the amount of the agent required varies slightly from one bacterial

FIG. 6. Photomicrograph of crystals of graminic acid. × 320.
(Reproduced by courtesy of Dr. R. D. Hotchkiss)

species to another. On the contrary, the Gram negative bacilli are resistant to graminic acid, gramidinic acid and gramicidin. Recent experiments have established that gonococci and meningococci are more resistant than the Gram positive organisms but more susceptible than the Gram negative bacilli; it is of interest to point out in this respect that, although meningococci and

gonococci react negatively to the Gram stain, they are very different in other respects from the Gram negative bacilli.

The standard test used for estimating the activity in vivo of the preparations of bactericidal substance has consisted in determining the minimal amount of substance which, when injected intraperitoneally within 30 minutes after infection, will protect mice against 10,000 fatal doses of Type I pneumococci.

In spite of the great bactericidal activity which graminic and gramidinic acid exhibit in vitro, these substances appear to be ineffective in vivo. On the contrary, one single dose of 0.001 to 0.002 mg. of gramicidin, injected into the peritoneal cavity, is capable of protecting mice against 10,000 fatal doses of pneumococci or hemolytic streptococci. The material has been found equally effective against infection with five different types of pneumococcus, 11 types of Group A streptococcus and three strains of Group C streptococcus; other types were not tried (table 2).

TABLE II

Protective Action of Crystalline Fractions of Bactericidal Agent

(All mice infected with 10,000 fatal doses of Type I Pneumococcus)

Material	Amount	Number of mice	Result		
	mg.				
Graminic acid	0.016	3	D40	D44	D68
Graminic acid	0.008	3	D40	D40	D48
Graminic acid	0.004	3	D40	D40	D40
Graminic acid	0.002	3	D40	D96	D96
Graminic acid	0	3	D24	D40	D40
Gramicidin	0.010	3	S	S	S
Gramicidin	0.005	3	S	S	S
Gramicidin	0.002	3	D61	D114	S
Gramicidin	0.001	3	D45	D46	S
Gramicidin	0	3	D27	D27	D32

S = Survival.
D = Death; the numeral indicates number of hours after infection.

By using larger doses of the bactericidal agent and repeating the treatment on three consecutive days, it has been possible to protect mice against 1,000,000 fatal doses of pneumococcus and to cure mice of a well established infection, even when treatment was administered 6, 12, and 17 hours after injection of the infective dose.[7, 13]

The results which have just been reported demonstrate that gramicidin, when injected into the peritoneal cavity in mice, is very effective against infection with pneumococci and streptococci. However, the same substance when injected intravenously, subcutaneously, or intramuscularly, fails to protect mice against infection with the same organisms. Gramicidin is very insoluble in aqueous media and it is possible that it fails to diffuse and reach

the different foci of infection. This fact may account in part for its failure to act when injected at a site remote from the infected area.

In any case, it is obvious that the insolubility of the material in aqueous media is a great handicap both for experimental studies and for possible use in therapy. It has been recently found that a number of dispersing agents (such as sulphonated and sulphated oils) permit the substance to remain in solution in water even in the presence of electrolytes; ox bile also acts as a particularly effective dispersing agent, 2 c.c. being sufficient to maintain 10 mg. of gramicidin in solution.

Furthermore, it has been possible to extract from cultures of the soil organism which produces gramicidin a form of this substance which is completely soluble in water, without the help of dispersing agent. This soluble fraction is obtained by clarifying an autolysate of the peptone culture by centrifugation and filtration through a Berkefeld candle; the clear filtrate is then adjusted to pH 4.7 and the precipitate separated by centrifugation. This precipitate is again soluble in saline at neutral reactions; it gives the usual protein tests and exhibits marked bactericidal activity. When injected by the intraperitoneal route, 0.2 mg. is sufficient to protect mice against 10,000 fatal doses of pneumococci. Moreover, in a number of instances, it has been possible to cure mice of pneumococcus peritonitis and septicemia by the subcutaneous injection of 2.0 mg. of the same water soluble fraction. The methods of preparation of this new material and the technic of administration to experimental animals have not yet been perfected, so that the results of subcutaneous treatment are still very irregular; they are, however, unequivocal and show that it is possible to extract from cultures of the soil bacillus a form of the bactericidal substance which is more effective in vivo than the crystalline material described under the name gramicidin.

Much remains to be learned about the physiological activity of these substances, both upon the bacterial cells and in the mammalian organism. It has been shown that the bactericidal principle in its different forms (graminic acid, gramidinic acid, gramicidin, and the new water soluble fraction) interferes with some of the essential metabolic functions of the susceptible bacterial species.[8] It is also known that gramicidin exhibits a marked toxicity for mice, rabbits, and dogs when administered by the intravenous route, 3 mg./kg. being sufficient to kill a dog within 48 to 72 hours.[24] Any attempt to express the toxicity of the material in terms of its therapeutic efficacy would be misleading at the present time. It must be remembered in this respect that practically all the successful protection tests to date have involved the intraperitoneal treatment of pneumococcus and streptococcus peritonitis in mice; gramicidin has proved ineffective when administered by the intravenous, intramuscular, or subcutaneous route. The few successful results obtained by the subcutaneous administration of the new water soluble fraction are too preliminary and have been too irregular, to warrant generalization.

Discussion

It may be worth while to contrast again the mechanisms whereby the two types of microbial reagents which have been considered in the present report, protect experimental animals against bacterial infections.

The first group of reagents was obtained by isolating from soil, microorganisms capable of multiplying in solutions of the capsular polysaccharides of the different types of pneumococci. Cultures of these bacilli have yielded soluble enzymes, each one of which hydrolyzes one of the specific polysaccharides. Not only do the polysaccharidases decompose the soluble, isolated polysaccharides, but they also destroy the capsules which surround the virulent pneumococci, and protect animals against pneumococcus infections; these reactions are highly specific, the specificity being determined by the chemical nature of the polysaccharide which constitutes the capsule of the particular type of pneumococcus under consideration. The enzymes are neither bacteriolytic nor bactericidal; by destroying the protective capsular material of the pneumococci, they merely render them susceptible to the phagocytic action of the cells of the infected host.

In some respects, therefore, the polysaccharidases exert upon the infectious process an influence similar to that exerted by the specific antipneumococcus sera. Both types of agents prepare the encapsulated bacteria for phagocytosis, the antibodies by specific sensitization, the enzymes by the progress of decapsulation. In the former instance, the reaction is an immunological one whereby the capsular material is altered by union with the type specific antibody; in the latter case, the reaction is an enzymatic one which results in the actual decomposition of the polysaccharides. Neither the enzymes nor the specific antibodies are by themselves bactericidal or bacteriolytic, yet each, by reacting specifically with the capsular substances, exposes the virulent organisms to the phagocytic action of the body tissues.

Gramicidin, the other protective agent described in the present paper, has also been extracted from a sporulating soil bacillus, but does not appear to belong to the class of enzymes. It should rather be considered as a true antiseptic, minute concentrations of which inhibit the growth of the susceptible species in nutrient media, whereas higher concentrations exert an actual killing effect. It is likely therefore that the protective action induced in vivo by this new agent can be explained, in part at least, in terms of its bacteriostatic and bactericidal effect upon the susceptible bacteria.

Whereas the specific enzymes, like the specific antibodies, act upon a product of the bacterial cell, namely the capsular polysaccharide, the new bactericidal agent probably interferes with some essential metabolic function of the invading microörganisms; in this respect, the mechanism of its protective action presents some analogy with that exerted by the sulfanilamide group of drugs, which do not affect the capsular substances of pneumococci, but only inhibit the growth of the bacterial cells.

Gramicidin protects mice against infection with pneumococci, strepto-

cocci, and staphylococci, all bacterial species which are susceptible to it in vitro, and appears therefore to be entirely unspecific in its action. It must be emphasized again, however, that gramicidin is ineffective against Gram negative bacilli and for example fails to protect mice against infection with *Klebsiella pneumoniae*.

It can be said, therefore, that the new bactericidal agent exhibits a specificity of a peculiar order, one which is correlated with the staining characteristics of the bacterial cells. Since the staining properties are necessarily conditioned by chemical and physical characters of cellular structure, it is perhaps permissible to state that the specificity of the bactericidal agent is related to some unidentified structural difference between the Gram positive and the Gram negative cells. An analysis of the mechanism of the bactericidal action may therefore reveal important facts concerning cellular structure, and this knowledge in turn will suggest new avenues of approach to the problems of antisepsis. It is also of obvious importance to establish what are the chemical differences between graminic acid and gramicidin which determine that only the latter is active in vivo, whereas both are equally active in vitro; this knowledge may give us a clue as to the mechanism which allows an antiseptic to remain active in the presence of animal tissues, and suggest technics for the synthesis of new chemotherapeutic agents.

It is permissible to hope also that one will eventually discover in nature microörganisms capable of attacking other types of pathogens, or their toxic principles. By extracting from cultures of the soil organisms the active antibacterial or antitoxic principles, then determining their nature and the mechanism of their action, the bacteriologist and the chemist may discover new compounds, and new technics for the development of chemotherapy on a rational basis.

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THE COMPARATIVE EFFECTIVENESS AND TOXICITY OF SULFATHIAZOLE AND SULFAPYRIDINE IN PNEUMOCOCCIC PNEUMONIA *

By Harrison F. Flippin, M.D., Leon Schwartz, M.D., and S. Brandt Rose, M.D.,† *Philadelphia, Pennsylvania*

Following the discovery that sulfapyridine was an effective agent in treating experimental and clinical infections due to the pneumococcus, chemotherapy of pneumococcic pneumonia has received widespread attention during the past two years. Within this time numerous [1] clinical reports unquestionably have established the therapeutic effectiveness of sulfapyridine in pneumonia. However, it is generally recognized that sulfapyridine therapy is not ideal because nausea and vomiting often interfere with adequate treatment. Furthermore, serious toxic manifestations, such as blood dyscrasias and renal complications, may occur.

Within recent months there has become available a new sulfanilamide derivative, sulfathiazole,‡ which we have used in the treatment of patients suffering with pneumococcic pneumonia at the Philadelphia General Hospital. Sulfathiazole, 2-(p-aminobenzenesulfonamido) thiazole, synthesized by Fosbinder and Walter [2] and Lott and Bergeim,[3] is the thiazole analogue of sulfapyridine. The therapeutic effectiveness of sulfathiazole against experimental pneumococcic infections has been investigated by McKee, Rake, Greep, and Van Dyke [4] and found to be equal to that of sulfapyridine. Van Dyke, Greep, Rake and McKee [5] showed that sulfathiazole administered to mice with their food was no more toxic than sulfapyridine when the dose was kept at therapeutic levels.

In a recent report [6] observations on the pharmacology and toxicology of sulfathiazole in man were discussed. It was found that sulfathiazole was absorbed more rapidly than sulfapyridine from the gastrointestinal tract and was excreted more rapidly in the urine. Following the intravenous administration of sodium sulfathiazole recovery of the drug in urine was practically quantitative. Absorption of sodium sulfathiazole by rectum was slow and only 10 per cent was found in the urine within 24 hours.

The purpose of the present report is to compare the therapeutic effectiveness and toxicity of sulfathiazole and sulfapyridine in the treatment of pneumococcic pneumonia.

* Read before the American College of Physicians, Cleveland, April 3, 1940.

† With the collaboration of Jefferson H. Clark, M. D., and John G. Reinhold, Ph.D. From the Committee for the Study of Pneumonia, Philadelphia General Hospital.

‡ We are indebted to Dr. George A. Harrop, Squibb Institute for Medical Research, New Brunswick, New Jersey, for the sulfathiazole used in this study.

Selection of Cases

From the beginning of this study (November, 1939) the medical services * in the hospital were divided into two therapeutic groups, so that approximately an equal number of pneumonia patients received sulfathiazole or sulfapyridine. During this period of five months 152 patients were treated with sulfathiazole and 162 patients with sulfapyridine. In this report, our observations on the first hundred patients from each therapeutic group are presented. Of the 200 patients, 19 (10 sulfathiazole, 9 sulfapyridine) received specific antipneumococcus serum † in addition to chemotherapy.

Diagnosis

The diagnosis of pneumonia was established by the clinical history and the findings on physical examination. When indicated, the diagnosis was confirmed by roentgen studies. A specific pneumococcus type was recovered from the sputum or blood stream in all patients. Blood cultures were taken in 95 per cent of the cases, but some of these were not obtained until a few hours after treatment had been started. Repeated blood counts and urinalyses were made in all patients. Determinations of free and total drug in the blood were made in all patients receiving sulfathiazole and in most of of those treated with sulfapyridine. Other laboratory studies were made as indicated.

Sulfathiazole Dosage

Except in a few patients treated at the beginning of this study we employed the following dose schedule: An initial 3 gm. dose by mouth was repeated in four hours, then followed by 1 gm. every four hours. Several extremely ill patients were given three initial doses of 3 gm. each at four hour intervals. Dosage on this scale maintained an average concentration of free sulfathiazole of about 5 mg. per cent.[6] Treatment was continued until the temperature remained normal for 48 hours along with evidence of clinical improvement. In general, the total dosage was 25 to 40 gm., depending on the physical and laboratory findings in each case. Sodium citrate (or potassium citrate) in an amount equal to that of sulfathiazole was given with each dose of the drug. In certain instances, when a rapid elevation of the blood level of the drug was desired a 5 per cent solution of sulfathiazole sodium (0.06 gm. per kilogram of body weight), was administered, as a supplement to oral therapy. One intravenous dose was usually sufficient to raise the blood level of free sulfathiazole to 8 to 10 mg. per 100 c.c.

* We wish to express our thanks to the following Chiefs of Service for the clinical facilities they have given us for this study: Dr. R. S. Boles, Dr. H. D. Jump, Dr. T. Klein, Dr. D. W. Kramer, Dr. S. A. Loewenberg, Dr. D. Riesman, Dr. W. E. Robertson, Dr. H. W. Schaffer, Dr. T. G. Schnabel, and Dr. R. G. Torrey.

† The sulfapyridine and serum used in this study were supplied by the Pennsylvania State Department of Health, Pneumonia Control.

Sulfapyridine Dosage

The initial dose was 3 gm. by mouth, followed by 1 gm. every four hours until the required total dosage had been given. A total of 25 to 35 gm. was usually sufficient. As with sulfathiazole therapy the drug was given until the temperature had remained normal for 48 hours and satisfactory clinical improvement was noted. Sodium bicarbonate was given, in an amount equal to that of the drug, to most patients with each dose of sulfapyridine. Sulfapyridine sodium, 5 per cent solution (0.06 gm. per kilogram of body weight) was administered in conjunction with oral therapy when indicated. With sulfathiazole or sulfapyridine therapy at least 2500 c.c. of fluid were given during each 24 hour period.

Table I

Distribution of Types, Bacteriemia, and Mortality Rates

Type	Sulfathiazole Treated				Sulfapyridine Treated			
	All Cases		Bacteriemic Cases		All Cases		Bacteriemic Cases	
	Number	Died	Number	Died	Number	Died	Number	Died
I	17	2	1	1	23	3	3	—
II	6	1	1	1	2	—	—	—
III	25	4	3	1	22	6	3	3
IV	8	1	2	1	4	—	—	—
V	5	—	2	—	8	1	1	1
VI	4	1	1	—	3	—	—	—
VII	9	—	—	—	6	1	2	1
VIII	3	1	—	—	7	—	—	—
IX	—	—	—	—	1	1	—	—
X	1	—	—	—	3	—	—	—
XI	1	1	—	—	—	—	—	—
XII	1	—	1	—	2	—	—	—
XIII	1	—	—	—	1	—	—	—
XIV	9	1	2	—	4	1	1	1
XV	—	—	—	—	2	1	—	—
XVI	2	—	—	—	1	—	—	—
XVII	—	—	—	—	2	1	—	—
XVIII	2	—	—	—	3	—	—	—
XIX	3	—	—	—	1	—	—	—
XX	—	—	—	—	2	—	—	—
XXII	—	—	—	—	2	—	1	—
XXV	1	—	—	—	—	—	—	—
XXVIII	1	—	—	—	1	—	—	—
XXXI	1	—	—	—	—	—	—	—
Total	100	12	13	4	100	15	11	6
Mortality Per Cent	12.0		30.8		15.0		54.5	
Corrected Mortality Per Cent *	7.4		10.0		11.4		37.5	

* Does not include 9 patients (5 sulfathiazole and 4 sulfapyridine) who died in less than 24 hours after admission; 6 of these cases had bacteriemia (3 sulfathiazole and 3 sulfapyridine).

Serum Dosage

When sulfathiazole or sulfapyridine had apparently failed to bring about the expected clinical response within 36 to 48 hours the patient was usually given specific serum in addition. The usual preliminary sensitivity tests, conjunctival and intradermal, were always performed. If these were negative after 20 minutes, further intravenous testing with undiluted serum (1 c.c.) was carried out. After waiting 70 minutes for possible untoward

Table II

Analysis of Fatal Cases †

Sulfathiazole

No.	Age	Day of Disease Treatment Begun	Type	Blood Culture	No. of Lobes Involved	Total Drug	Total Serum	Remarks
yrs.	yrs.					gm.	units	
1	37	2	I	Neg.	2	18	100,000	Jaundice (ict. index 250 u.), anuria (B.U.N. 130 mg. %) and delirium tremens on adm. Autopsy: Acute toxic necrosis of liver, cholemic nephrosis, lobar pneumonia.
2*	42	7	I	Pos.	2	3	—	Moribund on adm., died in 8 hrs. Autopsy: Lobar pneumonia.
3	29	5	II	Pos.	3	30	320,000	No response to ℞. Autopsy: Empyema.
4	77	4	III	Neg.	1	12	—	Diabetes mellitus, cardiac decompensation. No autopsy.
5*	30	6	III	Neg.	2	3	—	Moribund on adm., died in 6 hrs. Autopsy: Lobar pneumonia, toxic degen. of adrenals.
6	77	3	III	Neg.	3	13	100,000	Cardiac decompensation. Autopsy: Broncho-pneumonia, cardiac hypertrophy, portal cirrhosis.
7*	47	10	III	Pos.	2	9	—	Moribund on adm., died in 10 hrs. Autopsy: Lobar pneumonia, luetic aortitis.
8*	42	5	IV	Pos.	2	9	—	Moribund on adm., died in 18 hrs. Autopsy: Lobar pneumonia.
9*	62	3	VI	Neg.	2	6		Moribund on adm., died in 15 hrs. Autopsy: Bronchopneumonia, acute coronary occlusion with myocardial infarction.
10	76	4	VIII	Neg.	2	50	100,000	Responded to combined therapy. T. normal for 72 hrs. before death. Cardiac decompensation. No autopsy.
11	52	3	XI	Neg.	1	15	—	Transferred from surgery. Projective vomiting. Intestinal obstruc.? X-ray: Lobar consolidation. No autopsy.
12	40	3	XIV	Neg.	1	22	—	Sputum typing delayed. No response to drug. Autopsy: Lobar pneumonia, nephrosclerosis, cardiac hypertrophy.

* Patient died within 24 hours after admission.

† Autopsy performed by members of the staff of Pathology of the Laboratories; chief Dr. H. M. Dixon.

TABLE II—*Continued*

Sulfapyridine

No.	Age	Day of Disease Treatment Begun	Type	Blood Culture	No. of Lobes Involved	Total Drug	Total Serum	Remarks
	yrs.					gm.	units	
1	78	6	I	Neg.	1	7	—	Moribund on adm., died in 28 hrs. No autopsy.
2	49	3	I	Neg.	2	16	—	Responded to ℞. Sudden death. No autopsy.
3*	55	9	I	Neg.	1	4	—	Moribund on adm., died in 14 hrs. Autopsy: Lobar pneumonia, cardiac hypertrophy.
4	67	2	III	Neg.	1	50	—	Normal T. for 5 days before death. Cardiac decompensation. Autopsy: Broncho-pneumonia, cardiac hypertrophy.
5*	50	8	III	Pos.	1	3	—	Moribund on adm., died in 6 hrs. Autopsy: Lobar pneumonia with abscess, toxic nephrosis.
6*	42	14†	III	Pos.	3	4	—	Moribund on adm., died in 21 hrs. Autopsy: Lobar pneumonia, portal cirrhosis.
7	50	3	III	Neg.	1	15	100,000	No response to ℞. Autopsy: Lobar pneumonia, marked coronary sclerosis, cardiac fibrosis and nephrosclerosis.
8	64	2	III	Neg.	2	13	—	Responded to ℞. Sudden death in 38 hours. No autopsy.
9*	49	5	III	Pos.	1	6	—	Moribund on adm., died in 18 hrs. Autopsy: Lobar pneumonia, cardiac hypertrophy and toxic degeneration of adrenals.
10	66	3	V	Pos.	1	26	600,000	No response to ℞. Alcoholism. Autopsy: Lobar pneumonia and nephrosclerosis.
11	42	8†	VII	Pos.	1	15	100,000	No response to ℞. Alcoholism, cardiac decompensation. No autopsy.
12	42	6	IX	Neg.	3	26	—	Responded to ℞. Normal T. for 36 hrs. before death. Autopsy: Lobar pneumonia, cardiac hypertrophy, nephrosclerosis.
13	32	1	XIV	Pos.	1	15	—	Before adm. jumped from third story window. Broken arm, fractured skull? Alcoholism. Moribund throughout hospitalization. No autopsy.
14	40	2	XV	0	2	24	—	Responded to ℞. Normal T. for 6 days before death. Cardiac decompensation. Autopsy: Lobar pneumonia, cardiac hypertrophy, mitral stenosis.
15	69	8†	XVII	Neg.	2	25	—	Cardiac decompensation. Autopsy: Broncho-pneumonia, bronchogenic ca. rectal carcinoma, cardiac hypertrophy.

reactions, and if none were detected, the patient was given an initial dose of 100,000 units of undiluted serum intravenously followed by further serotherapy when necessary.

Therapeutic Results

The results of treatment in the two therapeutic groups are shown in table 1. Of the patients treated with sulfathiazole, 12 died. In the sulfapyridine treated group there were 15 deaths. Patients who were moribund on admission and died within 24 hours were included in both therapeutic groups, although they did not provide a fair trial for either drug. Five such patients were treated with sulfathiazole and four with sulfapyridine. If these cases are excluded the corrected mortality becomes 7.4 per cent and 11.4 per cent for the sulfathiazole and sulfapyridine treated groups respectively.

Table III

Mortality According to Race and Sex

Race	Sex	Sulfathiazole Treated			Sulfapyridine Treated		
		Number	Died	Mortality %	Number	Died	Mortality %
White	Male	37	6	16.2	45	8	17.8
	Female	23	2	8.7	27	4	14.8
Negro	Male	29	3	10.3	23	3	13.0
	Female	11	1	9.1	5	–	—

Table IV

Mortality According to Age Groups

Age Group Years	Sulfathiazole Treated			Sulfapyridine Treated		
	Number	Died	Mortality %	Number	Died	Mortality %
12–19	11	–	—	7	–	—
20–29	20	1	5.0	10	–	—
30–39	17	2	11.8	19	1	5.3
40–49	23	4	17.4	25	6	23.0
50–59	13	1	7.7	20	3	15.0
60–69	9	1	11.1	14	4	28.6
70 and over	7	3	42.9	5	1	20.0

Thirteen patients with bacteriemia were treated with sulfathiazole and four of these died. If the three bacteriemic patients dying within 24 hours are excluded the corrected mortality in this subgroup is 10.0 per cent. In the sulfapyridine treated group, 6 of the 11 bacteriemic patients died, and if the three 24 hour cases are excluded the corrected mortality becomes 37.5 per cent. In both therapeutic groups the unusually high incidence of Type III infection has probably raised the mortality (tables 1 and 2). However, of the 10 fatal Type III patients 4 were 24 hour deaths (2 sulfathiazole, 2 sulfapyridine). Therefore, the corrected mortality values are less affected by the high incidence of this type of infection.

In tables 3 and 4 the distribution of cases according to sex, race, and age groups is given with the mortality per cent. In general, these factors are comparable in the two therapeutic groups. Table 5 shows the incidence of mortality in relation to the day of disease when treatment was begun. Although a greater number of sulfathiazole patients were treated during the first three days of the disease, this does not appear to have had a decided influence on the comparative mortality rates of the two therapeutic groups. Of the 12 fatal cases treated with sulfathiazole, seven patients were treated after the third day of the disease and four of the deaths occurred within 24 hours after admission. In the sulfapyridine treated group eight of the 15 deaths occurred in patients treated after the third day of the disease and five of this number died in less than 24 hours after admission.

TABLE V

Mortality in Relation to Day of Disease on Which Treatment Was Begun

Day of Disease When Treatment Begun	Sulfathiazole Treated		Sulfapyridine Treated	
	Number	Deaths	Number	Deaths
1	13	–	3	1
2	24	1	21	3
3	21	3	19	3
4	14	3	19	0
5	12	2	14	1
6	4	1	9	2
7	6	1	5	–
7+	6	1	10	5

INFLUENCE OF TREATMENT ON THE COURSE OF THE DISEASE

Table 6 shows the effect of treatment on the temperature in the two therapeutic groups (all deaths excluded). A critical drop in temperature occurred within 24 hours in 50 per cent of the patients treated with sulfathiazole, as compared to 65.8 per cent of the patients in the sulfapyridine treated group. At the end of 48 hours 88.6 per cent of the patients receiving sulfathiazole showed a critical drop in temperature compared with 95 per cent of the patients treated with sulfapyridine. The temperature fell to normal, within 24 hours, in only 6.8 per cent of the patients in the sulfathiazole treated group and in 21.2 per cent of the patients receiving sulfapyridine. Within 48 hours normal temperatures occurred in 45.4 per cent and 70.6 per cent of patients in the sulfathiazole and sulfapyridine groups respectively. A secondary rise in temperature occurred in 18 patients (6 sulfathiazole, 6.8 per cent; 12 sulfapyridine, 14.1 per cent) and these usually required further drug therapy. Cases in which a diagnosis of drug fever was made are not included in this group. The average number of hospital days for patients in each therapeutic group is practically the same, 13.2 days. Not included in the latter group are all deaths and 27

TABLE VI

Effect of Treatment on Temperature and Hospital Stay

Critical Fall in Temperature *	Sulfathiazole Treated			Sulfapyridine Treated		
	Number	per cent		Number	per cent	
Within 24 hours	44	50.0	88.6	56	65.8	95.2
Within 48 hours	34	38.6		25	29.4	
Within 72 hours	7	8.0		2	2.4	
Over 72 hours	3	3.4		2	2.4	
Temperature at normal level *						
Within 24 hours	6	6.8	45.4	18	21.2	70.6
Within 48 hours	34	38.6		42	49.4	
Within 72 hours	20	22.8		14	16.5	
Over 72 hours	28	31.8		11	12.9	
Secondary Rise in Temperature (above 99° F.) *	6	6.8		12	14.1	
Average Stay in Hospital †	13.22 days			13.21 days		

* All deaths excluded.

† Not included in this group are all deaths and patients kept in hospital for further study and treatment of accompanying conditions.

patients (12 sulfathiazole, 15 sulfapyridine) who remained in the hospital for various conditions (empyema, paresis, diabetes mellitus, heart disease, etc.).

As mentioned above, type specific serum was used in addition to chemotherapy in the treatment of 19 patients. The results are shown in table 7.

TABLE VII

Chemotherapy Plus Serotherapy in 19 Cases

Distribution of Types, Bacteriemia, and Mortality

Type	Sulfathiazole Treated				Sulfapyridine Treated			
	All Cases		Bacteriemia Cases		All Cases		Bacteriemia Cases	
	Number	Died	Number	Died	Number	Died	Number	Died
I	1	1			3		2	
II	2	1	1	1				
III	3	1	1		2	1		
IV	1							
V					1	1	1	1
VII	1				2	1	2	1
VIII	1	1						
XIV	1		1					
XVIII					1			
TOTAL	10	4	3	1	9	3	5	2

Of the 10 cases in the sulfathiazole-serum treated group, four died. In the sulfapyridine-serum treated group of nine patients, three died. This group of 19 patients included eight bacteriemias, with three deaths.

In every instance that serum was used we were of the opinion that drug treatment had apparently failed to bring about the expected clinical response within 36 to 48 hours. We realize that the value of combined therapy is questionable at present, but until sufficient data are presented to prove it definitely less effective than chemotherapy alone we feel justified in the combined use of serum and drug in selected cases. It is our impression that the administration of serum was a deciding factor in the recovery of several patients.

Complications

The incidence of complications (table 8) in both therapeutic groups was small and comparable. Massive pleural effusion occurred in three patients treated with sulfathiazole and in two patients receiving sulfapyridine. Empyema was present in only three patients, once in the sulfathiazole

Table VIII

Incidence of Complications (200 cases)

Complications	Sulfathiazole treated Incidence per cent	Sulfapyridine treated Incidence per cent
Massive effusion	3.0	2.0
Empyema	1.0	2.0
Phlebitis	—	1.0
Metastatic abscess	1.0	—

treated group and twice in patients treated with sulfapyridine. One patient in the sulfapyridine group developed phlebitis and one patient in the sulfathiazole group suffered a metastatic abscess of the lower abdominal wall which was successfully drained.

Toxic Reactions

The most frequent untoward effects of both drugs (table 9) were nausea and vomiting. Both symptoms appeared usually during the first 24 hours of treatment. The vomiting associated with sulfathiazole therapy was unlike the severe and persistent vomiting caused by sulfapyridine; it was mild and infrequent and was marked by absence of severe nausea between attacks. In four patients receiving sulfapyridine it was necessary to discontinue therapy because of severe vomiting. In no case did nausea or vomiting necessitate discontinuance of sulfathiazole therapy. It is noteworthy that of the 20 cases of vomiting in the sulfathiazole series fully 13 of these (mild vomiting) vomited only once or twice during the entire course of therapy.

Microscopic hematuria was detected in six patients receiving sulfathiazole and ten patients treated with sulfapyridine. Gross hematuria was observed

in only one instance, in a sulfapyridine treated case. No cases of anuria or renal pain were noted in either group. After treatment with sulfathiazole or sulfapyridine, crystals, presumably of these drugs, have occasionally been observed in the urine. A study of the comparative effect of sulfathiazole and sulfapyridine on the kidney is in progress and the findings will be reported at a later date. However, our observations at this time suggest that although there is a rather frequent reduction in kidney function during treatment with these chemotherapeutic agents, the effect appears to be transient. A return to normal even before cessation of therapy usually occurs. Nevertheless, the possibility of serious renal damage from sulfapyridine, and probably from sulfathiazole, must be borne in mind in the light of experimental and clinical reports.[7, 8, 9, and others]

TABLE IX

Incidence of Toxic Reactions (200 cases)

Toxic Reactions		Sulfathiazole Incidence %	Sulfapyridine Incidence %
Nausea		25.0	84.0
Vomiting *	Mild	13.0	12.0
	Moderate	7.0	40.0
	Severe	0.0	4.0
	Total	20.0	56.0
Hematuria	Microscopic	6.0	10.0
	Gross	0.0	1.0
	Total	6.0	11.0
Dermatitis		4.0	2.0
Drug fever?		2.0	4.0
Psychosis?		4.0	7.0

* Includes 15 patients (8 sulfathiazole, 7 sulfapyridine) who were vomiting before treatment was started. Mild—less than three times; Moderate—three or more times; Severe—necessitated stopping drug.

Dermatitis, apparently caused by the administration of these drugs, was noted in four patients (two were maculopapular and two were urticarial) receiving sulfathiazole and in two patients (maculopapular) treated with sulfapyridine. One patient, treated with sulfathiazole, not included in this series, showed a mild conjunctivitis associated with a drug rash.

The question of drug fever is difficult to evaluate in pneumonia patients, although six cases (two sulfathiazole, four sulfapyridine) apparently showed this condition. Likewise, psychosis is difficult to attribute to the use of chemical agents in an acutely febrile disease such as pneumonia. However, we have encountered 11 patients (four sulfathiazole, seven sulfapyridine) whose symptoms appeared to be due to the drug.

Repeated blood studies failed to show any evidence of a marked reduction in hemoglobin, red blood cell or white blood cell counts. There were

no cases of hemolytic anemia or agranulocytosis in either therapeutic group. However, in the majority of cases the white blood cell count tended to drop during the first 48 hours coincident with the drop in temperature in both groups. The red cell count and hemoglobin likewise fell in a number of cases, but in view of the marked dehydration of most of our patients on admission it has been difficult to evaluate this apparent secondary anemia.

Because of the nature of the disease process, no attempt was made to evaluate the production of cyanosis in either therapeutic group. This condition was comparatively infrequent.

Comment

In view of our experience thus far, sulfathiazole and sulfapyridine appear to be equally effective in the treatment of pneumococcal pneumonia. The mortality of 12 per cent (corrected to 7.4 per cent) in the group of 100 sulfathiazole patients and of 15 per cent (corrected to 11.4 per cent) in the comparable sulfapyridine series compares favorably with the previous mortality rate of approximately 35 per cent at the Philadelphia General Hospital [10] in the years preceding the use of these chemotherapeutic agents.

As evidenced by the critical fall in temperature within 24 hours sulfapyridine appeared to be the faster acting drug, although at the end of 72 hours the effect of both drugs on the temperature was practically the same. With either drug the drop in temperature was usually accompanied by a corresponding subjective and objective improvement of the patient. Significantly, the average stay in the hospital was the same in both therapeutic groups, 13.2 days.

The incidence of complications was very low in this series of 200 cases and was approximately the same in both the sulfathiazole and sulfapyridine treated patients.

Nausea and vomiting, which are so distressing and often troublesome with the administration of sulfapyridine, were much less marked in frequency and severity in the sulfathiazole group. Also, there was some evidence that other toxic manifestations of sulfathiazole were less severe.

At this time we are of the opinion that serum is indicated in selected patients who fail to respond to chemotherapy within 36 to 48 hours.

Summary

1. Sulfathiazole was given to 100 patients with typed pneumococcal pneumonia and a comparable series of 100 patients were treated with sulfapyridine.

2. There were 12 deaths in the sulfathiazole series, five of which were hospitalized for less than 24 hours (corrected mortality 7.4 per cent). In the sulfapyridine series there were 15 deaths, four of which were hospitalized for less than 24 hours (corrected mortality 11.4 per cent).

3. Sulfapyridine brings the temperature down somewhat more rapidly than sulfathiazole, although the average number of hospital days for the two therapeutic groups was the same, 13.2 days.

4. The severity and frequency of nausea and vomiting in the sulfathiazole treated patients was much less than in those patients receiving sulfapyridine. Other toxic manifestations were approximately equal in the two groups and were not severe.

We wish to acknowledge the technical assistance of Miss Beatrice Doak who was detailed for this and related studies on pneumonia by the Pennsylvania State Department of Health, Pneumonia Control.

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STUDIES IN MUCOUS MEMBRANE HYPERSENSITIVENESS. IV. THE ALLERGIC REACTION IN THE PASSIVELY SENSITIZED MUCOUS MEMBRANES OF THE ILEUM AND COLON IN HUMANS *

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In a previous communication [1] the allergic reactions, occurring in the passively sensitized mucous membranes of the stomach, ileum and colon of the Rhesus monkey, were described. Edema, hyperemia and increase in the secretion of mucus characterized all of these reactions. In these features, the reactions in the mucous membranes of the monkey were very similar to those which had been observed in the passively sensitized mucous membrane of the rectum in humans.[2]

The present communication deals with allergic reactions occurring in the passively, locally sensitized mucous membranes of the ileum and colon *in humans*. These studies were made on two non-atopic individuals who gave the following histories:

Patient X was a male, aged 52, who had been operated upon in June 1936 for a carcinoma of the rectosigmoid portion of the colon. A preliminary transverse colostomy was followed by a resection of the involved bowel with primary anastomosis. The mucous membrane of the colostomy at the time of the present studies (April 1937) showed a moderate amount of congestion.

Patient Y was a male, aged 22, who had been operated upon in March 1937, for a perforating, non-suppurative terminal ileitis. A two-stage Mikulicz operation had been performed. The patient presented an exteriorized ileo-colostomy. The mucous membranes of the ileum and colon at the time of the present investigations appeared normal except for a slight amount of congestion.

Technic

For the study of the allergic reactions in the human ileum and colon the authors employed a technic very similar to that which they had previously used in their investigations on the human rectal mucous membrane.[2] The first step of the procedure consisted of the sensitization of the mucous membranes of the exposed colon and ileum to peanut protein by the intramucosal injections of a human serum containing atopic reagin antibodies for peanut. After an interval, varying from 24 to 36 hours, peanut antigen was fed to the patients on a fasting stomach. Within several minutes an inflammatory reaction developed at each of the sensitized mucous membrane sites indicating the entrance of unaltered peanut protein into the circulation. The reactions

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of the mucous membranes at the sites of sensitization were the result of the union of the circulating peanut antigen with the reagin antibodies to peanut, which had been injected into the mucosa and had remained fixed in these areas.

A. Passive local sensitization of the mucous membrane of the ileum and colon.

1. *Sensitizing Serum:* The choice of a peanut serum for sensitization purposes was accidental and was determined by the circumstance that a suitable serum of this type happened to be available at the time. It was obtained from an asthmatic patient who manifested an unusually strong cutaneous reaction to a skin test with peanut antigen. This serum showed a very high titer for reagin antibodies to peanut antigen (1 to 1024 by the dilution method of Coca and Grove [3]). It was used in a dilution of 1 to 10 for sensitizing the mucous membranes in order to prevent the development of a too severe allergic reaction in these tissues.

2. *Sites of Sensitization:* The mucous membrane of the colon in patient X was sensitized about two or three inches from the skin edge of the colostomy. In patient Y, the mucous membranes of both the ileum and the colon were sensitized from one and one-half to two inches from the skin edge. In both subjects cutaneous sites on the arm were also sensitized with the peanut serum for purposes of control and comparison. When the same subject was used repeatedly for different experiments, care was exercised to use different areas of mucous membrane for sensitization.

3. *Technic of Sensitization:* All nuts and similar antigens were excluded from the subject's diet for the duration of the experiment, beginning 24 hours previous to the sensitizing injection. About 0.05 c.c. of a 1:10 dilution of the sensitizing serum was injected into each mucous membrane site. A 27 gauge needle was employed for this purpose. The procedure was not accompanied by any subjective symptoms and was not followed by any bleeding.

B. Administration of the Protein Meal.

From 24 to 96 hours after sensitization, the allergic reaction in the bowel was induced by one of the following procedures: (1) Oral administration of the antigen. (2) Introduction of the antigen through a catheter into the lumen of the exposed bowel. (3) Direct application of the antigen on a cotton applicator to the sensitized site of the mucous membrane. The antigen was administered in the form of a peanut "milk," made by dissolving 10 grams of raw ground peanuts in 30 c.c. of water, to which was added one gram of sugar and 0.05 c.c. of oil of cloves.

The details of some of the most important experiments are presented herewith in chronological order.

Studies Performed on Patient X with Colostomy

The allergic reaction *induced by oral administration of the antigen.*

Experiment I. April 1, 1937. 10:00 a.m. A site on the mucous membrane of the colon and a cutaneous site on the arm are sensitized to peanut by injections of 0.05 c.c. of human serum, containing peanut antibodies, according to the technic described above.

April 3, 1937. 9:45 a.m. The peanut meal is administered orally. 9:50 a.m. The sensitized mucous membrane site is becoming pale and there is an increase in the secretion of mucus over this area. 9:53 a.m. The pallor over the sensitized site is pronounced. It is surrounded by a zone of pink erythema. The remainder of the exposed bowel retains its original congested appearance. 9:55 a.m. The affected area of mucous membrane appears pale pink, is edematous, and presents an oozing surface. It has lost its normal granular appearance. It appears tense and there is an absence of the normal mucous membrane folds. The increase in the secretion of mucus is marked. 9:56 a.m. The patient reports the onset of pruritus at the sensitized cutaneous site on the arm at this time. This is followed within the next four minutes by the complete development of a large wheal and a surrounding erythema which completely cover the sensitized area. 10:00 a.m. A prominent, tense, crescent-shaped, pale, edematous area now covers the sensitized site on the mucous membrane of the colon. Marked secretion of mucus continues from this surface. 10:10 a.m. Edema at the sensitized mucous membrane site is still pronounced and the oozing of mucus continues. 10:14 a.m. The reaction at the mucous membrane site shows signs of subsiding. The mucous membrane folds are beginning to reappear. 10:20 a.m. The edema is rapidly diminishing but the outline of the crescent-shaped edematous area is still clearly visible. 10:25 a.m. The pinkish pallor of the affected site is disappearing. This area still appears tense and feels slightly indurated. 10:30 a.m. The edema is gradually subsiding. 10:40 a.m. The mucous membrane at the sensitized area is slowly regaining its normal granular markings. Some edema is still present. 11:00 a.m. A slight amount of edema may still be detected at the mucous membrane site. 11:12 a.m. The patient reports a recurrence of the pruritus at the cutaneous site on the arm and of the skin in the region of the colostomy. This symptom is mild and transient. 11:20 a.m. Except for a slight degree of edema, the mucous membrane at the sensitized site is almost normal in appearance. Folds are now present in the mucous membrane and its color is approaching that of the surrounding bowel. 11:45 a.m. A slight amount of edema is still detectable at the site of the reaction. Otherwise the bowel is practically normal.

Experiment II. The allergic reaction induced *by the introduction of the antigen into the exposed lumen of the colon.*

April 21, 1937. 9:00 a.m. A site on the mucous membrane of the colon and a cutaneous site on the arm are sensitized according to the technic described above.

April 25, 1937. 10:47 a.m. A rubber catheter is inserted through the colostomy opening into the lumen of the gut for a distance of about 5 inches. Five cubic centimeters of peanut "milk" are then introduced, through the catheter, directly into the lumen of the bowel. 10:51 a.m. The subject reports the onset of pruritus at the sensitized cutaneous site on the arm. Within two minutes a large wheal and surrounding erythema develop at this site. 10:52 a.m. Pallor and edema are evident at the sensitized mucous membrane site of the colon. 10:56 a.m. The edema of the colon site is marked. The normal mucous membrane folds are absent. The area appears tense. The increase in the secretion of mucus is pronounced. 10:56 to 11:30 a.m. The reaction develops in a manner similar to that described in Experiment I. 11:30 a.m. The reaction at the mucous membrane site is beginning to subside. 12:05 a.m. A slight amount of edema is still visible.

Experiment III. The allergic reaction induced *by the direct application of the antigen to the sensitized area of the mucous membrane.*

May 3, 1937. 2:00 p.m. A site on the mucous membrane of the colon and a cutaneous site on the arm are sensitized according to the technic previously described.

May 5, 1937. 5:00 p.m. A cotton applicator is dipped into the peanut "milk" and brushed lightly across the sensitized mucous membrane site of the colon. 5:05 p.m. The subject reports the onset of pruritus at the sensitized cutaneous site on the arm. This is followed by the appearance of erythema at this area within the next minute and by the onset of wheal formation a minute later. 5:05 p.m. A small bleb is present on the surface of the sensitized mucous membrane site of the colon. 5:07 p.m. The mucous membrane site is pale and edematous. 5:11 p.m. Edema and hypersecretion of mucus are pronounced in the affected area of mucous membrane. From this point on the reaction continues to develop in a manner similar to that described in the previous experiments.

Studies Performed on Patient Y with Ileo-Colostomy

Experiment IV. The allergic reaction *induced by the oral administration of the antigen.*

May 3, 1937. 2:00 p.m. A cutaneous site on the arm and mucous membrane sites on both the ileum and the colon are sensitized according to the technic described above.

May 5, 1937. 4:50 p.m. The peanut meal is taken orally. 4:54 p.m. The subject notes a transitory burning sensation in the region of the ileo-colostomy. This disappears within one minute. 4:55 p.m. An erythema accompanied by pruritus is noted at the sensitized cutaneous site on the arm. Within 4 minutes a large wheal surrounded by erythema develops in this area. 4:56 p.m. A small bleb, surrounded by pale mucous membrane is present at the sensitized mucous membrane site of the ileum. The colon mucous membrane site remains unchanged at this time. 4:58 p.m. The pallor over the ileum site is spreading. Pallor is also beginning to develop at the colon site. Both mucous membrane sites now show definite edema and hypersecretion of mucus. 5:03 p.m. Both the ileum and colon sites are pale, markedly edematous and protrude several millimeters above the level of the contiguous bowel. The normal mucous membrane folds are absent over these areas which are from 1.5 to 2 cm. in diameter (see figures 1 and 2). 5:10 p.m. The edema at both mucous membrane sites continues to increase. Mucous hypersecretion in these regions is still pronounced. 5:14 p.m. The edematous mucous membrane areas are now from 2½ to 3 centimeters in diameter. Hyperemia has replaced the pallor at these sites. Increased mucous secretion still continues. From this point, the progress of the reactions is the same as in previous experiments.

Experiment V. The allergic reaction *induced by the introduction of the antigen* into the joint lumen of the ileo-colostomy.

May 10, 1937. 11:00 a.m. Mucous membrane sites of the ileum and colon and a cutaneous site are sensitized according to the technic previously described.

May 12, 1937. 12:56 p.m. Four and one-half c.c. of peanut "milk" are introduced into the joint lumen of the ileo-colostomy. 1:00 p.m. Erythema appears at the sensitized cutaneous site on the arm. A large wheal and erythema, accompanied by pruritus, develop within the next five minutes. 1:04 p.m. The ileum and colon sites show a slight pallor. A slight tenseness of the mucous membranes in these areas is also present. 1:05 p.m. The sensitized mucous membrane areas of both the ileum and colon are markedly edematous and bulge as if inflated with air. There is a pronounced excess of mucus secretion from these surfaces. The normal mucous membrane folds over the reacting areas are obliterated by the edema. From this point, the reactions develop in a manner similar to those described in the previous experiments.

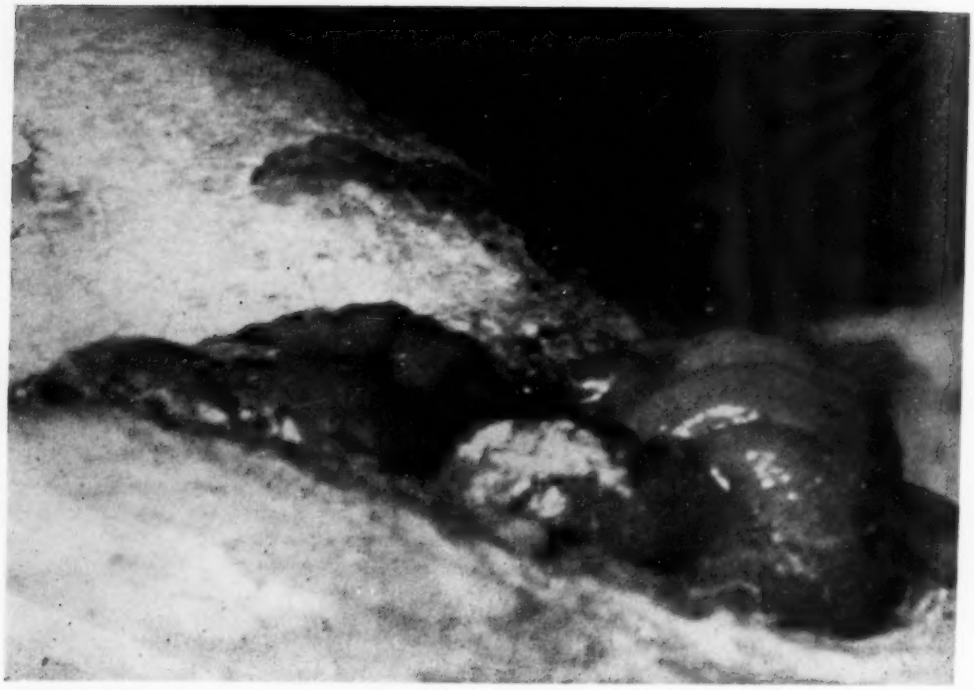

FIG. 1 (Case Y). Normal appearance of mucous membranes of exteriorized ileo-colostomy. Ileostomy on left. Colostomy on right.

FIG. 2 (Case Y). Ileum and colon sites at height of allergic reactions. Note marked edema of ileum mucous membrane (left) and colon mucous membrane (right) with obliteration of normal mucous membrane folds. Pallor and mucous hypersecretion also observed at this time.

The Allergic Reaction at the Passively Sensitized Mucous Membrane Sites

Pallor of the mucous membrane and an increase in mucous secretion were usually the first objective signs of the allergic reaction as it developed at the sensitized mucous membrane sites. Within one or two minutes the development of edema obliterated the normal mucous membrane folds and markings. The edema usually reached its height within from 15 to 20 minutes and persisted for one or more hours. Although it started at the site of sensitization it diffused to a slight extent into the surrounding area. The pallor which characterized the early part of the reaction was gradually replaced by hyperemia. The reaction was always confined to that region of the mucous membrane which had been sensitized to the specific antigen which was administered.

Examination of the mucus secreted at the site of the reaction failed to reveal an increase in the number of eosinophiles.

Itching and a slight burning sensation of the skin around the colostomy and ileo-colostomy were occasionally reported by the subjects during the course of the reactions.

Discussion

It has been shown in previous investigations that the mucous membranes of the eye,[4] nose [5] and rectum [2] in humans and the mucous membranes of the stomach, ileum and colon in the Rhesus monkey [1] may be passively and locally sensitized by the injection of human reagin-bearing sera. In the present communication the writers have demonstrated that the mucous membranes of the ileum and colon in humans may be similarly sensitized.

The characteristics of the allergic reaction in the passively sensitized mucous membranes of the ileum and colon are essentially the same as those observed in the sensitized mucous membranes of the stomach, ileum, and colon in the Rhesus monkey and as those noted in the passively sensitized mucous membrane of the rectum in humans. Edema, hyperemia and increased secretion of mucus are the primary features of all of these allergic mucous membrane reactions.

In the present study, the allergic reactions were elicited by the oral or enteral administration of the antigen or by its direct application to the sensitized mucous membrane site.

It is interesting to note that the mere touching of the mucous membrane with a cotton applicator, holding about 0.1 or 0.2 c.c. of peanut "milk," was sufficient to induce a cutaneous reaction in from 4 to 5 minutes. From this incident, one may appreciate what minute amounts of absorbed antigen can produce severe general allergic reactions.

After the administration of the peanut meal the allergic reactions developed at the sensitized cutaneous sites within from 4 to 11 minutes and at the sensitized mucous membrane sites of the ileum and colon within from 5 to 8 minutes. In four of the six experiments, the cutaneous reaction pre-

ceded the mucous membrane reaction in onset by from 1 to 4 minutes. The reactions in both regions, however, seemed to reach their maximum at about the same time. The fact that the mucous membrane, despite its direct contact with the antigen, did not react maximally until the antigen became generally disseminated by way of the circulation had been previously noted by the authors in their rectal mucous membrane studies.[2] It further emphasizes the importance of the general absorption of the antigen in the production of localized allergic reactions of the bowel. It suggests the probability that the most severe crises in gastrointestinal allergy result from excitation of the sensitive shock tissues by the absorbed and circulating offending allergen. The mere application of the antigen to the sensitive wall of the organ does not in itself seem capable of eliciting the maximal allergic reaction of the sensitive mucous membranes.

Conclusions

1. The mucous membranes of the ileum and colon in humans can be passively and locally sensitized by the intramucosal injection of human reagin-bearing serum.

2. The allergic reaction can be induced at these sensitized areas by the oral administration of the antigen, by its introduction into any part of the bowel or by its direct application locally to the sensitized mucous membrane sites.

3. The allergic reaction in the passively sensitized mucous membrane of the ileum or colon in humans is characterized by edema, hyperemia and excessive mucus secretion.

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THE VISCEROSPINAL SYNDROME—A NEW CONCEPT OF VISCEROMOTOR AND SENSORY CHANGES IN RELATION TO DERANGED SPINAL STRUCTURES *

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NEW concepts in physiology are most often developed in the course of animal and laboratory experimentation. This thesis, however, will trace an apparently new development in physiological thought produced and elaborated through clinical studies since 1925.

The existence of radiation phenomena as the result of radiculitis, "intercostal neuritis," and parietal muscle spasm due to disturbances in the region of the spine, is now generally accepted by clinicians,[1, 2, 3] more particularly by orthopedic surgeons and less universally by the internist. Two chief considerations have been stressed in this "radicular syndrome," viz: (1) cutaneous hyperesthesia and tenderness in the distribution of the spinal segment involved, and (2) muscle spasm or atrophy of muscle groups in the somatic periphery related to this segment. To these concepts may be added a third or *visceral* component.

It is this visceral component and its apparently unrecognized rôle in the body economy that I intend to discuss in this paper. A preliminary consideration of the subject in relation to spinal curvatures was offered in 1933 [4] and the term "viscerospinal syndrome" was used to describe the physiological changes in the viscera produced by essentially the same factors as cause the parietal radiation phenomena. Typical cases were presented in which symptoms of appendicitis, gall-bladder disease, ureteral colic or other manifestations of visceral disease were apparently relieved by correction of a spinal curvature or of the associated myositis. In the main I was convinced that the variations in the visceral symptomatology depended on the various spinal levels involved. Gall-bladder colic and cardiospasm, for example, were shown in some instances to be related to myositis in the middle dorsal area. Symptoms of appendicitis or pelvic inflammation were shown to be definitely associated with irritation of the lower dorsal segments. In these cases physiotherapy and postural correction were sufficient in most instances completely to relieve the patient of the visceral disorder.

This concept was considered somewhat radical in that it pre-supposed certain efferent impulses to the viscera to be initiated by changes in the somatic structures in and about the vertebral column. The actual anatomical pathway for such impulses was denied or at least not sufficiently recognized, except perhaps by a few physiologists.[5, 6] Since then, however, a number of

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investigators have clearly demonstrated the possible anatomical and physiological connections between the autonomic fibers found in the skin, dorsal musculature and vertebral articulations on the one hand and autonomic fibers innervating the viscera on the other.[7] The pathways involved will be described later.

In the preliminary report it was stressed that symptoms produced by visceral changes were not to be confused with hyperesthesia of the skin over the viscus. Intercostal neuralgia produced by osteoarthritis of the spine or by localized myositis near the spine related to the same cord segment was also a factor to be ruled out. Superficial somatic involvement of this type has been described by numerous writers beginning with Dejerine[8] and his "radicular syndrom." Carnett[8] attempted to differentiate "parietal neuralgia from the intra-abdominal lesions which it simulates." Pottenger[9] has repeatedly demonstrated the various skeletal changes brought about by diseases of the lungs and pleura. Furthermore the detailed studies by Gunther and Kerr[10] of the radicular type of pain involving the parietal portions of the body have focused the attention of most clinicians on the *external* manifestation of this radiation phenomenon. Possibly due to the failure of the above writers to visualize an adequate nerve pathway for a visceral involvement no consideration was given to this vital component.

My aim in this presentation is to add to and elaborate upon the observations made in the early studies of this syndrome; to correlate the whole by grouping the different visceral components with the related segmental levels of the nervous system, and to establish the syndrome as important in the differential diagnosis of visceral disease.

More than 400 instances of this syndrome have been encountered. Of these at least 40 per cent have shown multiple manifestations of the syndrome depending on the various segmental levels involved. Most of these patients had been treated without success by one or more physicians who have used the standard medical procedures. To simplify the study an arbitrary grouping of the segmental areas and their related viscera has been made. As far as possible each division is introduced by a description of the particular nervous mechanism involved and completed by a discussion of the physiological changes in the viscus under study.

A brief picture of the fundamental principles of the pertinent neuroanatomy is offered as a general introduction. This is to do away with repeated descriptions of the subject in each succeeding section.

Nervous Mechanism

It may clarify the syndrome to describe the probable nerve pathways involved. The apparent simplicity of their arcs makes it difficult to understand the insufficient recognition of their fundamental rôle. In general, afferent impulses from the skin, the dorsal musculature or the articulations of the vertebral column are relayed through the cord and emerge as efferent

impulses to the viscera. Possibly a more direct route exclusive of the spinal tracts is available but this must be determined by the physiologist. The afferent fibers are mainly of the somatic sensory type and carry impulses from such skin structures as the cutaneous blood vessels (figure 1, A), the secreting glands, and the erector pilae muscles.[9] The afferent impulses (figure 1, B) from the dorsal musculature are also somatic sensory and originate in the muscle spindles.[10] Sympathetic efferent fibers to the muscles are confined in their distribution to the intramuscular blood vessels.[11] It is

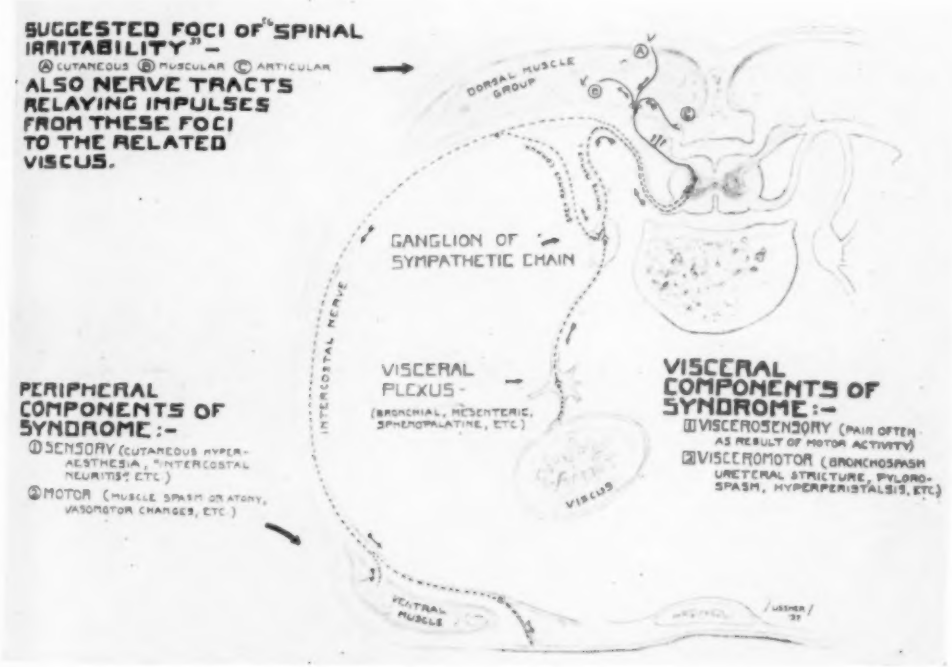

FIG. 1. Diagram showing chief components of viscerospinal syndrome. Suggested foci of irritability ("A," "B," "C") are depicted from which afferent impulses are carried to the cord by dorsal nerve roots. Synaptic connections are shown relaying the impulses through the ventral roots to the viscus by way of the viscero-efferent sympathetic network.

not clear whether afferent impulses originate from these also.[12] The third component of the syndrome (figure 1, C), namely the vertebral articulation, is richly supplied by a sympathetic network containing somatic afferent fibers. Impulses may originate from the peri-articular blood vessels or from the ligamentous attachments. Proprioceptive fibers may be considered an integral part of this group.

These various afferent fibers converge and probably pass into the cord via the dorsal nerve roots and spinal ganglia. Here short synaptic connections allow the afferent impulses to be transmitted to efferent fibers incorporated in the ventral roots of the spinal nerves. Preganglionic fibers now

act as the carriers through the *rami communicantes* to the sympathetic ganglia of the abdominal chain. New synaptic connections in these ganglia allow the transmission of the efferent impulses to the viscera by way of the postganglionic neurons. In some cases the preaortic ganglia, such as the coeliac or mesenteric, act as a final way point for these impulses before the viscus is reached.

It must be remembered that a tremendous literature has grown up concerning the nervous pathways related to the conduction of impulses *from* the viscera. The mechanism of referred pain and changes in the skeletal structures due to visceral disturbances has been widely discussed.[13, 14, 15, 16, 17] It is not within the province of this paper to deal with this phase except to stress the importance of recognizing the viscerospinal syndrome as essentially concerned with a *reversal of the process* that pictures the impulses as originating in a viscus and thence being referred to somatic or skeletal structures.

Head

Orthopedists have repeatedly demonstrated that pain in the occiput and posterior auricular regions may be related to cervical scoliosis and myositis involving the cervical and extreme upper dorsal muscle groups.[18] Their attention, for the most part, has been directed exclusively to the areas innervated by the cervical *somatic* nerve groups, such as the great occipital branches from the second and third cervical nerves. That pain in areas conforming to the distribution of the sphenopalatine and vidian nerves—the orbit, the posterior nasopharynx and the maxillae—may result from the above dorsal and cervical irritations is a point apparently neglected by the orthopedists and the otorhinolaryngologists alike. Sluder and others[19, 20] have minutely described pain caused by direct stimulation of the ciliary, sphenopalatine, and otic ganglia. The clinical causes of such pain, in their viewpoint, were nearby lesions affecting the ganglia; the rôle of distant lesions was not considered. If no cause, such as infection in or about the ganglia, was found, the term "idiopathic neuralgia" was frequently used. Vail[21] has elaborated on Sluder's studies by describing a neuralgia brought on by sphenoid sinus infection, associated with the vidian nerve and its distribution. This neuralgia is characterized by a "sharp deep pain in the root of the nose radiating in, about, and behind the eye, over the temple to the ear and the mastoid process to the back of the head and neck, and in severe cases passing into the shoulders and arms." No mention is made of the possibility that a focus of irritability more distant than an adjacent sinus could initiate the train of symptoms. The present study suggests that there are more remote foci which may consist of myositis of the cervical and upper dorsal group of muscles, chilled cutaneous structures in this area, or articular derangements of the cervicodorsal spine. The sympathetic network as well as the somatic nerve groupings act as the probable channels for these rela-

tively distant foci. It has been repeatedly demonstrated in this study that correction of factors causing irritation of these sympathetic fibers results in complete relief of symptoms. Conversely, after such a correction has been made the visceral symptoms may again recur if the myositis, or spinal maladjustment, is allowed to return.

Case 1. H. M. C., a moderately obese white married woman of 37.

Family History: Irrelevant except for death of father due to Bright's disease.

Past History: Usual childhood diseases; pneumonia (type not known) at 6 and 16 years of age. Frequent attacks of tonsillitis followed by a tonsillectomy in 1930. Patient developed rightsided pain shortly after this associated with intrascapular soreness. The pain was thought to be related to her gall-bladder. This was removed along with her appendix. However, both were found to be normal at operation and the patient soon had a moderate recurrence of her symptoms.

Present Illness: The patient was referred to the clinic by a dentist in September 1933. Her chief complaint was a dull aching pain in the right upper jaw and temporomandibular joint. The teeth on that side were hypersensitive to dental examination. The pain was fairly constant and had persisted for about a year. At times it became sharp and was noted along the right side of the nose and back of the right eye. She consulted several oculists for her symptoms and also had her right inferior maxillary nerve injected without relief. Two apparently normal teeth were also extracted with similar lack of relief. The patient found aspirin and sedatives of many varieties to be less effective than hot moist towels applied to the back of her neck. On waking in the morning the pain was usually absent. Toward evening the pain was invariably worse than earlier in the day. On questioning, the patient stated that she was worried about her failure to get relief for her condition and that she feared a mental breakdown if the pain continued. Being quite intelligent, she was anxious to convince her husband as well as herself that this condition was not a psychoneurotic manifestation.

Physical Examination: The essential findings were as follows: A thick-set, moderately obese woman of 37; dry skin, especially over the extremities; old right rectus scars of abdomen. Examination of the area of complaint (the right face and jaw) showed no definite abnormality either in appearance or in tenderness on pressure. However, a possible hyperesthesia of the skin of the right cheek was noted. (The patient often held, rubbed, or supported her face on that side, and little significance was attached to this finding.)

A sharp cervicodorsal angulation was found and an antero-posterior curve compensating for a lumbar lordosis. A pelvic tilt to the left was also observed. At the seventh cervical spine considerable muscle spasticity of the trapezius was present. Tapping on the cervical prominence with the index finger caused the patient to wince and cry out. She stated that some of her pain in the lower jaw and cheek was reproduced by this procedure. She could not locate the pain definitely but showed evident distress.

Treatment and Progress: A quarter-inch total heel lift on the left foot erased most of the lateral scoliosis. Mild postural exercises in the supine position using the infra red ray and massage of the spastic muscles relieved the cervical tenderness within three days. The pain involving the right face and teeth disappeared completely within six days. To facilitate postural correction, weight reduction and thyroid medication were started three months later. There were slight recurrences of pain several times during the next five months when she was particularly fatigued. An additional left heel lift of one quarter inch with continued exercises eradicated the remaining symptoms, and she has remained free of these up to the present writing.

To illustrate the acute involvement of the sphenopalatine network as contrasted with the chronic type a brief summary of one case is herewith presented.

Case 2. A. W., a man of 45, was seen at the clinic in December, 1933. He complained of severe pain in the naso-pharynx and was sure that he had an "abscess of the throat." The soft palate and posterior portion of the hard palate were also designated by the patient as areas of soreness. However, no evidence of local hyperemia, abscess or generalized infection was found, although light stroking of the soft palate with a cotton swab was quite painful. A few hours before the onset of symptoms the patient had driven about a hundred miles in a coastal fog with the car window open at his side. He had returned with a stiffness of his neck and a sensation of chilling about the occiput. He paid little attention to these symptoms particularly when the pain in the throat became dominant.

Treatment and Progress: As no local evidence of infection was found and appreciable stiffness and tenderness of the neck were present, infra red irradiation and light massage of this area were used. The pain in the palatal areas was markedly intensified by this procedure during the heat treatment. But it diminished and almost completely disappeared in a few minutes after massage of the cervical muscles. The last trace of "sore throat" was gone after a second treatment the following morning.

Note: No appreciable scoliosis was found in this patient to account for myositis or articular irritation in the cervical region. Cutaneous chilling in itself may have been of importance as a source of afferent impulses to the sympathetic and sensory network of the palate and naso-pharynx.

Comment

That a causal relationship exists in the above cases between the deep facial symptomatology and disturbances in and about the cervical region seems reasonable. The exact pathway of these pain impulses is undoubtedly variable and may consist of sensory or sympathetic fibers or both. Once the gap is bridged between external points of sympathetic irritation in the cervico-dorsal region (cutaneous, muscular or articular irritation) and the internal sympathetic network we can easily trace the pathways of the reflex arc. (Figure 1.)

Efferent sympathetic nerve impulses that form this internal network probably pass upward through the middle and superior cervical ganglia, thence along the carotid sheath and are distributed to one or more of the cranial ganglia, i.e., geniculate, otic, sphenopalatine, submaxillary, glossopharyngeal, etc. Synaptic connections within the ganglia thence allow efferent impulses to be distributed to such areas as the orbit, ear or maxillae. The patient experiences pain in these areas through stimulation of the higher centers of the brain by impulses transmitted along the afferent sensory pathways.

In describing vidian neuralgia as due to sphenoid sinus infection irritating sympathetic efferent nerves to the sphenopalatine ganglia, Vail [21] has clearly shown the reflex arcs involved from this point. He traces the impulse as leaving the "sphenopalatine ganglion along the efferent sympathetic nerves, through its orbital branches to the anastomosis which these

have with the terminal branches of the ophthalmic division of the orbit—through the sensory fibers in the great superficial petrosal nerve the stimulus is carried back to the geniculate ganglion. From the ganglion it is carried through the sympathetic efferent nerves of the geniculotympanic branch to the tympanic plexus. There it is taken up by the glossopharyngeal nerve and carried to the higher centers as pain in the ear. A severe stimulus or an overflow passes over the glossopharyngeal and vagus nerves or perhaps through the deep petrosal nerve to the superior cervical sympathetic ganglion and thence to the cervical sensory nerves and is perceived by the higher cortical centers as pain in the neck, shoulder and arm."

It has been demonstrated in this thesis, however, that the chain of nerve impulses may originate at foci other than the sphenoid sinus, although the end-results may be similar. The pain in the shoulder and neck may in some instances be more closely allied with the cause rather than with the effect of sympathetic nerve irritation. In other words, a cervico-dorsal irritation noticed by the patient as pain at the base of the neck, and observed by the physician as spasm and muscle tenderness of the upper border of the trapezius, may be the initiating factor in the train of symptoms known as vidian or sphenopalatine neuralgia (figure 2). Relief of this irritation by local physiotherapy or postural correction as above has been shown to result in a disappearance of the neuralgia.

That other pathways for this reflex pain must be considered is evident from the complexity of the autonomic and somatic nervous systems of the head and neck. Participation of the glossopharyngeal nerve, the cutaneous sensory branch of the facial nerve and many fibers of the fifth must be considered in reference to varying distributions of pain experienced by the patient.[22]

Interesting conjectures arise when considering the possible rôle of chronic sympathetic nerve irritation in hitherto unexplained trophic disturbances of such structures as the eye, sinuses, ear, etc. It must be admitted, however, that the field is extensive and complicated—that to control the observations adequately many more studies must be completed.

Lungs

The chief interest here lies in the possible relationship of the viscerospinal syndrome to bronchoconstriction, or asthma. Emphysema, pleurisy, and lung infections as possibly secondary to derangement of the autonomic nervous system have not been stressed in this particular investigation.

Not infrequently the physician observes a type of patient suffering from bronchial asthma of unexplainable etiology. Extensive protein sensitivity tests may be negative or at least inconclusive. The skin tests may, however, be positive but medical treatment consisting of desensitization to specific proteins and food elimination diets may give no relief. In very rare instances even the drugs used as specific dilators of the bronchial musculature are not sufficient and death may result.

That there is a definite correlation between tonal changes in the sympathetic nervous system and the bronchoconstriction of asthma has been repeatedly demonstrated by many physiologists. It has been shown, for example, that stimulation of the central ends of the thoracic sympathetics or of the communicating rami of the second and third thoracic nerves pro-

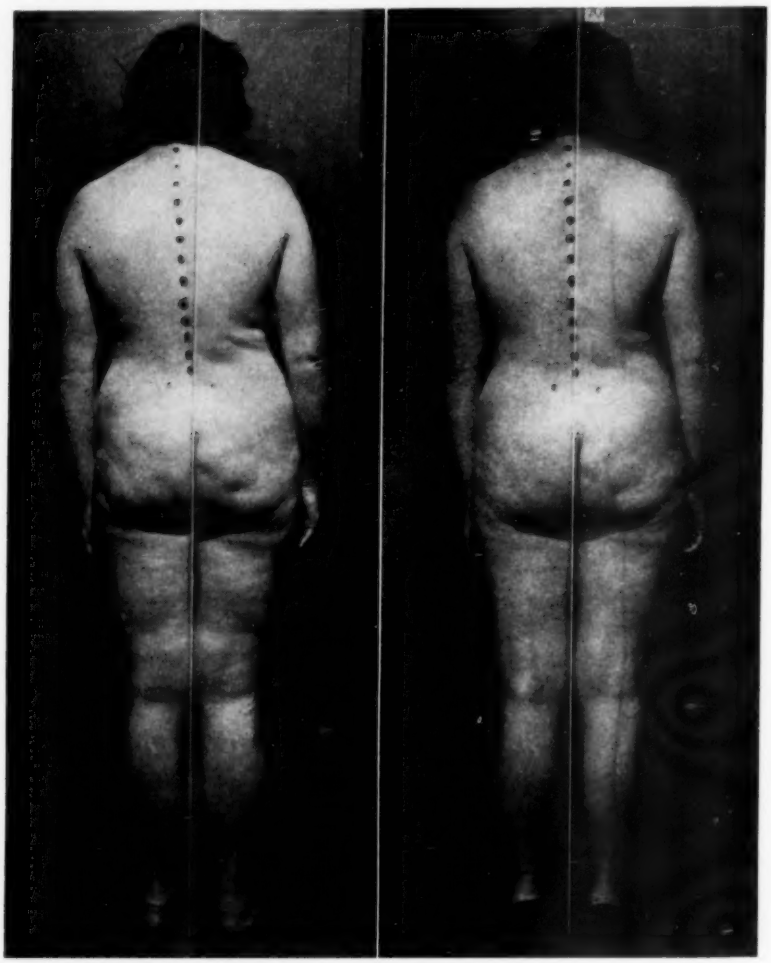

FIG. 2. (Left) Showing uncorrected posture of patient with long standing "sphenopalatine pain" related to cervicodorsal angulation. (Right) Partially corrected position following raise of left heel. Relief of pain noted a few days after correction. Return of symptoms when heel raise was discontinued four months later.

duces bronchoconstriction.[23] Stimulation of the central end of the vagus on the other hand may produce bronchodilatation.[24] It must be remembered that each lung has a bilateral as well as a bisystem supply and that extrinsic as well as intrinsic control is probably exerted by ganglia outside of and also within the bronchial tree.

White [25] attributes the paradoxical results obtained in experimental studies to the "intermingling of parasympathetic and sympathetic neurones in the thoracic vagus and sympathetic ganglia, as well as the relative autonomy of the intrinsic or the extrinsic ganglia of the lungs." He cites his own efforts and those of others to relieve bronchial asthma by interruption of the extrinsic pulmonary nerves. Results have been brilliant in some instances and questionable in others. In any case a consideration of explained and unexplained facts relative to the nervous regulation of bronchial tone leads one to believe that its control is one of the major aims of treatment. It would not therefore be surprising to find that the postulates of the viscerospinal syndrome hold true in certain types of asthma when disturbances of the nervous system in the upper segmental areas of the body occur (figure 1). That certain spinal curvatures, articular derangements and myosites of the dorsal musculature are often associated with the production of asthma has become increasingly evident to me during the past decade.

The possibility of such a relationship was first considered in 1925 when a patient at the New Haven Hospital volunteered the information that while undergoing heat therapy and massage for a muscle strain of his back some months previously he was completely relieved of a distressing asthma from which he had suffered for years. As he stated it, "My lungs were loosened up after a few minutes of the treatment and I was able to breathe freely and without discomfort." The physiotherapy was continued subsequently and the patient apparently had no recurrence of the asthma up to the time of my interview. His story was considered more dramatic than wholly within the facts of the case.

In 1928, however, a ward patient—a marked asthmatic and apparently in extremis—was admitted to my medical service in Providence, R. I. His case history in outline is herewith presented as an introduction to the subsequent studies.

Case 3. R. M., a well developed, rather obese Armenian, aged 38, was, when first seen, cold, cyanotic, straining weakly on expiration, and sweating profusely. Two Boston hospitals where he had been a patient several times during the preceding three years reported exhaustive protein sensitivity tests with no positive reactions. His hospitalization periods had ranged from 10 to 22 days, and moderate improvement had resulted from injections of large doses of adrenalin. In the intervals between periods of hospitalization, he had been forced to take 15 to 20 minims of adrenalin a day to obtain partial relief. In the attack, here described, adrenalin, ephedrine, atropine and calcium lactate were administered over a period of 24 hours with little relief, and the patient's heart became irregular in spite of digitalis and general supportive measures. As a last resort, remembering the New Haven incident, the physiotherapy department was requested to attempt a relaxation of the corded muscles of the patient's back. Heat and deep massage were applied to the whole back with especial attention to the region of the third, fourth and fifth dorsal vertebrae. Within eight minutes after this treatment was instituted the patient suddenly coughed up large plugs of mucus and what seemed to be bronchial casts, sank back in bed and began to breathe easily and almost without a wheeze. Six hours later a mild asthmatic attack occurred and was again relieved by a few minutes of massage and heat. Within two days he was dis-

charged in apparently excellent physical condition and advised to return for physiotherapy if attacks recurred.

Note: In addition to the above case there were six others ranging from 17 to 45 years of age seen at this hospital clinic who received partial or complete relief through physical therapy. Two patients were not benefited during two weeks of therapy and refused to return. Unfortunately I was unable to follow this first group of patients for more than a few months and do not feel justified in presenting them as typical cases.

Case 4. E. S., married, a Spanish woman, aged 33, was seen in the Santa Barbara Cottage Hospital dispensary on July 8, 1932 complaining of severe attacks of asthma during a period of eight years. She appeared acutely ill and unable to walk more than a few steps without resting. Her skin was cyanotic and moist. The lungs showed moderate impairment of resonance at both bases and were filled with large moist and sibilant râles. The heart sounds were distant and of poor quality. Systolic blood pressure 105, diastolic 75. An outstanding feature was a marked kyphosis of her upper spine and an inability to lift her head to the upright position without considerable effort. The muscles in the upper dorsal area were tense and spastic.

The positive findings in her history were as follows: whooping cough, mumps and frequent attacks of conjunctivitis in childhood. In 1925 she was accidentally immersed in cold water during a menstrual period. Following this she developed frequent and severe attacks of asthma. The attacks were brought on or aggravated by chilling drafts, or by dust. The attacks were also worse during the menses. In 1927 she had a tonsillectomy followed by a salpingectomy for "infected tubes." For the ensuing two years the asthma was not very troublesome and the patient believed she was recovering. However, in the fall of 1929 her attacks increased in severity and in frequency (10 to 12 attacks a day and three to five at night). Adrenalin and ephedrine compounds were used in increasing doses with relatively little benefit. Skin tests showed her to be sensitive to a number of foods and fall pollens, but the elimination of the foods did not apparently reduce the number or severity of attacks.

In September 1932 the patient was sent to the hospital physiotherapy department for corrective exercises to modify her kyphosis. Light massage of the upper back and the application of radiant heat were given about three times a week.

Progress: First month: The frequency of asthmatic attacks was reduced to two or three per week (previous to treatment they averaged more than 70 a week). The attacks, however, became more acute and developed more suddenly. Large amounts of mucus plugs were expectorated.

Second month: The attacks were reduced to one or two per week and seemed to be brought on by chilling in the late afternoon. The time of treatment was changed to the morning hours and improvement was noted.

Third month: The attacks continued, about one or two per week, but were milder and were immediately relieved by heat.

Fourth month: Patient had but one attack during the whole month. The exercises were stressed and a noticeable postural improvement was observed.

Fifth month: Two attacks occurred and in each instance the patient had slept with a window open at her head during cold and foggy weather. A definite swelling of the tissues about her neck and upper edge of the trapezius muscle developed in connection with the attacks. Heat and massage relieved this condition rapidly as well as the bronchoconstriction.

The patient now understands the necessary routine exercises and the general effect of chilling. Her general appearance and health are much improved at the present writing.

Case 5. W. C., male, white, aged 7. Seen by Dr. Howard Eder in the summer of 1931. This boy had developed a severe attack of asthma at one year of age—

followed by numerous attacks each year thereafter lasting four to eight hours at a time. The attacks were usually severe enough to keep him in bed for about a week. At three years he had extensive skin tests, all of which were negative except for a mild reaction to acacia. It was noted, however, that the asthma was not particularly aggravated during the flowering of the trees. Food elimination tests were entirely negative. No history of past illnesses except for mumps at three years.

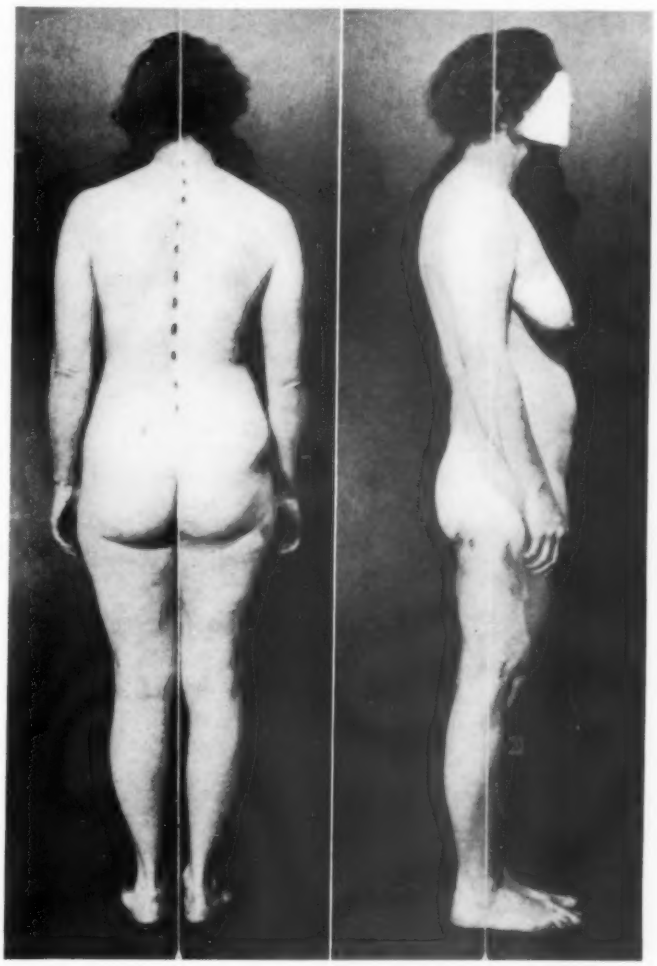

FIG. 3. Antero-posterior and lateral views of severe asthmatic patient before postural correction. Note dorsal scoliosis and kyphosis. Postural exercises were sufficient to maintain adequate relief not previously obtained by medication.

Postural exercises were instituted when it was noted that he had a definite dorsal scoliosis and lumbar lordosis. No heat or massage was used. The asthmatic attacks ceased completely within the first five weeks of exercises and have not recurred for the past 9 years. The boy's posture is markedly improved although a trace of the winged scapulae remains.

It is not clear why a correction of a spinal curvature should produce such a marked change in a boy whose asthma had been present as early as his second year.

for it seems hard to believe that posture is a factor at such an early age of development. However, it is a fact that the usual medical treatment remained almost valueless until postural correction was started.

Case 6. E. E., a housewife, white, aged 38 (figure 3), was seen at home in November 1932 during an incapacitating attack of bronchial asthma which was moderately relieved by ephedrine and amytal. Similar attacks had occurred with increasing severity for over a year and the patient dated the onset from a period of overwork at the laundry tubs. Her back had become tired and painful at the time and she had found it difficult to sit or stand "straight." The asthma was worse at the menses or when she was particularly nervous. She was not seen again for six weeks but during this time used prescribed sedatives and ephedrine compounds with very little benefit. The attacks increased in frequency and severity and she was examined at our clinic. The lungs were full of sibilant râles and wheezes. Expirations were markedly prolonged and difficult. Heart sounds of fair quality. Systolic blood pressure 155, diastolic 100. Examination of her back showed a definite dorsal kyphosis and long dorsolumbar scoliosis. The infrascapular musculature was spastic and tender on pressure.

She had suffered most of the childhood diseases and had undergone operations for bilateral inguinal herniae in 1930. Both her father and mother were known to have arteriosclerotic heart disease. In addition her mother and one of two brothers had hay fever and asthma.

Corrective exercises and physical therapy were started immediately after the examination. Within two weeks the patient believed her asthma to be entirely cured and refused to return for the radiant heat and massage. However, she continued faithfully with her exercises and remained free of all asthmatic symptoms for two years. Our physiotherapist made the interesting observation that at the time of her third visit the patient was suffering from a definite attack which was relieved during treatment. Immediately afterward the patient was able to walk home, a distance of more than a mile.

In February 1933, after illness in her family which necessitated considerable nursing attention on her part, she suffered a moderate attack of asthma. This was quickly relieved by the usual physiotherapeutic measures. Since then the patient meets any tendency toward recurrence of attacks by the renewal of her postural exercises.

Comment

In presenting the above cases of asthma an attempt has been made to keep in mind the numerous etiological possibilities in each individual. It is realized asthma often disappears spontaneously. It is realized that children "outgrow" asthmatic attacks in many instances. Bronchial neuroses do occur, as do reflex asthmatic attacks following disturbances of the sexual apparatus.[7]

However, when a group of persons suffering from long-standing asthma have been given the accepted medical treatment without receiving adequate relief some other procedure must be attempted. If a definite cessation of symptoms follows a new form of therapy this therapy should receive credit for the relief in a certain percentage of the cases. There may be a coincidence in one, in two, or even in three cases but not in a group of 10 or more.

It is evident that in many of the cases studied there was a relationship between asthmatic attacks and chilling. Horton and Brown [26, 27] have re-

ported a number of cases in which there were general as well as local symptoms due to cold allergy. It is their opinion that severe urticaria and asthma may be produced by a histamine-like substance released by the skin when certain individuals are exposed to chilling. Their observations corroborate the findings of Duke,[28] in the study of apparent allergic reactions to cold. Whether or not such a reaction is partially responsible for the asthma in the cases herein reported I am not prepared to say. It is suggested, however, that cold does produce a myositis or spastic contractions of the dorsal muscles. This may cause a change in tonus of the sympathetic nerves to the bronchial tree resulting in a general spasm and closure of the small bronchioles. Mucus and alveolar detritus may fill these stenosed lumena and if the asthmatic condition continues over a long period of time there may occur in certain instances proliferation of fibrous tissue about these inclusions even to the degree of a complete and permanent closure. C. K. Mallory has clearly demonstrated this pathological state in postmortem examinations of patients dying of asthma.

It is my opinion that the majority of bronchoconstrictions in the group presented here are due indirectly to some form of muscle spasm or myositis of the upper dorsal area. This myositis may be produced by direct trauma, by chilling, or as a result of a spinal curvature with irritation of the associated musculature. (Figure 1.) It seems reasonable to suppose that muscle in a state of irritable contractility exerts some effect on the sympathetic network, ganglia or chains in its neighborhood provided there are intercommunicating branches. This intercommunication is well recognized. Therefore I believe in some cases myositis and bronchoconstriction can be definitely correlated through the related nerve pathways.

Another feature is the benefit some patients derive from physical therapy in spite of their sensitivity to specific proteins. This is seen in Case 2, for example, a patient who reacted favorably to treatment though nothing was done to desensitize her or to remove the offending protein by elimination diets. The explanation for this is not clear.

The question arises as to whether the treatment of these cases resembles that offered by the manipulative cults, and the literature has been examined with that point in view. In 1925, Dr. Wm. P. Murphy[29] of Boston collaborated with an osteopath in the study of 20 cases of asthma that had formerly received careful vaccine therapy in the outpatient department of the Peter Bent Brigham Hospital without appreciable benefit. A series of so-called "adjustments" was given by various osteopaths once a week for an average of 70 treatments per patient. It was found in the follow-up study that 10 of the 20 patients had experienced about 50 to 100 per cent relief, either because of fewer attacks or less severe symptoms during attacks. In four of these the attacks were "practically stopped." The remaining patients were not appreciably benefited. It is interesting to note that the osteopaths were not in general accord as to the supposed location or the type of

disturbance involved but the general opinion favored a so-called " lesion " in the region of the fourth and fifth dorsal vertebrae. Treatment consisted of pressure on the transverse processes of these vertebrae and the rib attachments in that area. From our study it seems probable that favorable results were obtained in these cases not through the attack upon a single " lesion " but by obtaining relaxation of the spastic musculature involved. It is quite possible that the osteopath in his relaxation of muscle spasm has obtained results similar to those seen in our patients who showed such definite improvement after physiotherapy. Unless he recognizes the rôle of postural defects in asthma, however, and corrects them along definite orthopedic lines, results will be but temporary.

It would appear then that a suggestive relationship has been established among postural defects, myositis of the upper dorsal areas and bronchospasm. Recurrences of asthma should and do develop in cases where the postural exercises or corrections have been neglected. Conversely the asthma in this type of patient can usually be relieved in a remarkably short time again, and for an indefinite period if physiotherapy, exercises or orthopedic corrections are reinstituted.

Heart

In any discussion of the neurogenic mechanism of the heart three main nerve groupings should be taken into account:

1. Sensory nerves. 2. Motor nerves related to changes in heart rate. 3. Vasomotor nerves concerned with coronary dilatation or constriction. The nerves of these three groups are primarily sympathetic and consist of the network connected with the cervical ganglia (superior, middle, and inferior cervical) and with the upper four or five thoracic ganglia. In attempting to interrupt the sensory pathways surgical removal or paravertebral alcohol injections of these ganglia have been carried out with varying results. White [30] in a series of 40 cases of angina pectoris treated by paravertebral injections of alcohol showed that the method was capable of giving excellent results in two-thirds of his patients. In the majority of the remainder the severe forms of angina were converted into milder types which could be easily controlled by medical measures.

When considering the motor pathways, destruction of the accelerator fibers from the stellate and upper thoracic ganglia has also been shown to help in restoring normal rhythm in cases of paroxysmal tachycardia.

In reference to the third components of the extrinsic cardiac nerves, namely the vasomotor nerves involving the coronary circulation and possibly the greater vessels of the heart, numerous experiments would suggest that the caliber of the coronary arteries is directly under their control. There is also probably some indirect effect on the coronary flow through changes in the muscular activity of the heart.[31, 32] Humoral mechanisms must also be considered.

This brief description of the cardiac nerves is given to lay the groundwork for consideration of the viscerospinal syndrome in relation to the heart. The rôle of the sympathetic network in and about the spine and dorsal musculature has apparently not been recognized by investigators in this field. Our clinical observations, however, suggest that in some cases involvement of the parietal structures (skin, intercostal nerves, intercostal muscles) of the upper dorsal segments of the body may be intimately associated with the development of certain cardiac arrhythmias or changes in the coronary circulation. That this assumption seems bold and unorthodox I cannot deny, but it is consistent with observations of the viscerospinal syndrome in other segmental areas of the body.

In this cardiac group have been placed patients showing derangement of vertebral structures (dorsal scoliosis, kyphosis, or myositis) and in addition one or more of the following phenomena: (1) Intercostal neuralgia radiating to the precordial region, and usually designated by the patient as "heart pain." (This parietal manifestation in itself is of little significance but may be mistaken even by the physician for the pain of angina.) (2) Spasticity or atrophy of the pectoral or intercostal muscle groups. (3) Sensory and motor disturbances of the heart itself as indicated by true coronary or anginal pain; by dyspnea (usually transient); by paroxysmal tachycardia or other changes in the heart rate.

Naturally the cardiac symptoms are the most important and yet by their complexity are the most difficult to unravel.

In attempting to carry out an adequate study we are faced with the vagaries of the patient's subjective descriptions of precordial and radiation pain, and of the various neurotic elements in the "heart conscious" patient. In the diagnosis of angina the description of the subjective symptoms is of major importance but the objective findings are often helpful. They consist of the physical signs (changes in pulse, blood pressure, evidence of shock, etc.), cardiographic tracings, and possibly changes in circulation time.

To date the protocols of most of the patients studied in our clinic, as falling into this group are not sufficiently complete for presentation. However, several cases, one of which is offered below, have been under observation for a sufficient length of time to be of some value in this study.

Case 7. B. F. N., active, stocky business man of 40.

Family History: Father died of "hemorrhage of throat." Mother living but thyrotoxic. One brother has asthma.

Past History: Measles, mumps and whooping cough as a child. "Double pneumonia" at 22 years of age. Tonsillectomy at 31 and an appendectomy at 32 years. Bullet wound in right orbit with loss of vision in right eye at 35 years. Periodical vertical headaches every two months for 20 years up to removal of appendix. (He believes, however, that headaches were related to food sensitivity.)

Present Illness: The patient was first seen at the clinic in July 1934. At this time he complained of severe pressure in his chest and pain radiating down his left arm. There was also a sensation of fullness and pressure in his occiput and ears. These attacks of distress were fitful, occurring at intervals of two to three weeks and lasting

from one to three days. The attacks were usually accompanied by interscapular back pain. Exercise which produced sweating was found to relieve his symptoms to some extent, but on "cooling off," especially toward evening, they would tend to return. He felt very fatigued during the attacks. He usually smoked 40 cigarettes and drank one to three highballs a day. No particular change in his condition was noted when these were stopped. Often driving a car in cold weather or for long distances brought on the attacks within 24 to 48 hours. This was accompanied at times by severe coughing and vomiting of large amounts of mucus. His appetite was good and his bowels regular. He complained of nocturia two to three times. His sleep was fitful and often required barbiturates.

Examination: The essential point in his examination was the kyphosis. He appeared fatigued but outwardly calm. His pharynx was definitely injected from excessive smoking. No evidence of focal infection was evident in his sinuses, teeth or prostate. On examination of the chest wall intercostal tenderness along the fourth rib was noted on the left, also an area of extreme tenderness about the size of a silver dollar near the fourth spinous process. Some rigidity of the long dorsal muscles upward from this point and along the left border of the spine was found. Marked dorsal kyphosis and a lateral cervicodorsal curve apparently contributed to this area of irritation. A pelvic tilt to the left may have been another factor in the production of the lateral curvature. His lungs were clear except for occasional sibilant râles and wheezes. Percussion did not reveal cardiac enlargement although an orthodiagram suggested left ventricular hypertrophy and a Danzer ratio of 0.50. The sounds were of good quality. No murmurs were audible. His apical and radial pulses were 76. The systolic blood pressure was 140, the diastolic 95. His exercise tolerance was good. Electrocardiographic studies showed a moderate left axis deviation. A slight elevation of the S–T_1 and S–T_2 segments was evident. T_3 was inverted. Except for a relaxed abdomen, no gross abnormalities were noted in the remainder of his examination. The reflexes were within normal limits throughout.

Laboratory: The blood picture, including the Wassermann test, was negative. The urine showed a faint trace of albumin and occasional hyaline cast on repeated specimens. Roentgenograms of the gastrointestinal tract in August 1934 showed a hypertonic, steer-horn type of stomach, but no other abnormalities were noted. The basal metabolic rate was + 10.

Treatment and Progress: Nitroglycerin and codeine were given for precordial pain without appreciably influencing the course of the attacks. Saturated solution of potassium iodide produced some possible benefit, but the attacks persisted. Postural exercises were instituted for the dorsal curvature of the spine, but the patient did not adhere to his program. Shortly after this he returned from a week's trip to Seattle with a report of having suffered there a severe anginal type of pain and dyspnea. This persisted until some manipulative procedure by an osteopath gave him relief. The treatment was apparently directed toward the upper dorsal spine. A milder attack the following day was relieved in the same manner.

No evidence of coronary occlusion was found by electrocardiographic studies at our clinic three days after this episode.

Alimentary Canal

One of the most interesting applications of the viscerospinal syndrome is found in disturbances of the gastrointestinal tract. In 1933 I presented a preliminary report [4] in which it was shown that spinal curvatures involving the mid-dorsal spine could be associated in some instances with sensory and motor disturbances of the stomach and intestines. Subjectively these consisted of colicky pain, sense of fullness, bloating, and nausea. The motor

element was found in hyperperistalsis of the intestines, pylorospasm, vomiting (with or without nausea) and spastic constipation. A number of illustrative cases were reported wherein correction of the offending scoliosis had resulted in relief of symptoms.

Following this preliminary report over 200 cases illustrating this segmental response have been observed in the clinics and dispensaries of Santa Barbara. In most instances the syndrome was primarily related to the alimentary tract but involvement of other segmental areas of the body was found. In other words spastic constipation due to a lumbar myositis might be accompanied by a sphenopalatine neuralgia related to a cervical scoliosis, both symptoms in turn due to responses at different segmental levels to double scoliotic curves.

In this presentation it would be of value to elaborate more fully on the individual sections of the alimentary tract, and to add the newer observations related thereto. For convenience of study, I shall divide the tract into four parts, viz., the esophagus, the stomach, the small and large intestines, and the sigmoid and rectum.*

The Esophagus. In this study the esophagus acts as a transitional link between the viscera of the chest and the viscera of the abdomen as indicated by its sympathetic and parasympathetic nerve supply. In tracing the autonomic pathways to the heart and also to the bronchial tree it was noted that most of the sympathetic fibers were derived from the upper thoracic and lower cervical ganglia.[7] The parasympathetic passed through the vagus. Essentially the same neurological pathways are found in the innervation of the esophagus. Branches from the inferior cervical ganglion, from the upper four or five thoracic ganglia and from the greater splanchnic nerve form the sympathetic network. The vagus supplies the parasympathetic fibers.

As we are primarily interested in the clinical application of the viscerospinal syndrome the effect of stimulation of these nerves is of interest. Cardiospasm or achalasia of the cardiac sphincter of the esophagus is produced by such stimulation. Experimental studies, however, are not in full accord as to the exact rôle of either the vagus or the sympathetic elements. The vagus like the sympathetic supply to the cardiac sphincter includes both motor and inhibitory fibers. If the muscle is relaxed or in a state of low tonus, vagus stimulation results in contraction. If the sphincter is closed it results in relaxation thus opening the cardiac orifice.[34]

Four cases of cardiospasm have been classified in our series under the viscerospinal grouping. Three had symptoms of concomitant autonomic nerve disturbances related to the upper dorsal segments or other segmental

* In considering additional applications of the syndrome, I believe a study of the extrinsic and intrinsic secretions of the pancreas would be of value. The pancreas is richly supplied by autonomic fibers. De Takats and Cuthbert[38] have shown that sugar tolerance has increased 60 per cent in dogs following sympathetic denervation and suggest that a direct inhibitory effect on the secretion of insulin is probable in these instances. Mellanby[39] in very complete studies of pancreatic secretion has demonstrated the effect of vagus stimulation which increases the trypsin and amylase content of the pancreatic juice.

areas affected by the same postural defects. In the remaining patient the cardiospasm was the outstanding complaint.

Case 8. White, male, aged 37 (previously reported in 1933 in relation to gastro-intestinal and genito-urinary disturbances of viscerospinal type). The chief complaints during the past two years (1936–1937) were frequent attacks in which solid food seemed to "stick" just before passing into the stomach. At times he was forced to regurgitate food by touching the pharynx before relief was obtained from the accompanying pain. Large amounts of collected mucus along with the food bolus were thus evacuated, but a feeling of discomfort and soreness in the lower sternal area often remained. He noticed that the attacks were most severe shortly after playing golf and taking a shower. They seemed to be related to some chilling and discomfort in the upper back and neck. The patient noticed that by drinking warm liquids quickly and in large amounts he was often able to forestall the painful "sticking" sensations caused by heavier foods. Part way through a meal most of the symptoms tended to disappear. Fatigue and nervousness added to the severity of the attacks.

Fluoroscopic examination with ingestion of a thickened barium meal showed a smooth spastic constriction of the esophagus several centimeters above the cardia which allowed the meal to pass with difficulty. A column of barium remained above this constriction for several minutes and the patient said he experienced the usual "sticking" sensation in his lower sternal region. No evidence of extrinsic or intfinsic tumor masses was visualized.

Examination of the upper dorsal area showed a moderate kyphosis and a high interscapular angulation. Pressure on the second and third dorsal spinous processes elicited considerable tenderness. Spasticity of the interscapular muscle groups was found, particularly on the left. There was also definite tenderness on pressure along the third and fourth intercostal nerves on the right.

Postural exercises aimed to correct a right shoulder drop and resulting dorsal scoliosis were sufficient to relieve most of the interscapular myositis and intercostal pain. Shortly thereafter the attacks of cardiospasm subsided. No medication was used in the form of sedatives or antispasmodics although a more rapid recovery would probably have resulted with such aid.

It is interesting to note that this patient has been under observation for the past eight years by our orthopedic and physiotherapy departments. His dorsal skeletal structures were found to be easily deranged due to a mobile vertebral column. Unless adequate postural exercises were adhered to along with the necessary heel corrections there was a return of scoliotic and antero-posterior curves. This in turn produced local myosites and radiation phenomena as described elsewhere.

Comment

It must be remembered that the diagnosis of cardiospasm or achalasia of viscerospinal origin is to be made only after other intrinsic or extrinsic etiologic factors have been ruled out. Neoplasms in the esophageal wall or impinging on its nerve supply, ulcers near the sphincter, foreign bodies within the lumen, neuroses and hysterical manifestations are all to be considered in making the diagnosis. However, in a "neurotic" patient with exaggerated nervous manifestations it does not follow that the basic autonomic disturbance in the upper thoracic segments is to be ignored. It should be recognized that anxiety and nerve tension can act as the sparks to initiate other physiological changes in an already irritated segmental level.

The Stomach and Pylorus. The second division of the alimentary tract in relation to the syndrome consists of the stomach and pylorus. Here again

the vagus supplies the parasympathetic fibers and the splanchnic nerves ending in the coeliac network supply the sympathetic fibers. The latter are derived chiefly from the fifth to the eleventh pairs of thoracic white rami. Conflicting opinions of investigators have been expressed as to the effect of stimulation of these nerves, but suffice it to say that disturbances in gastric

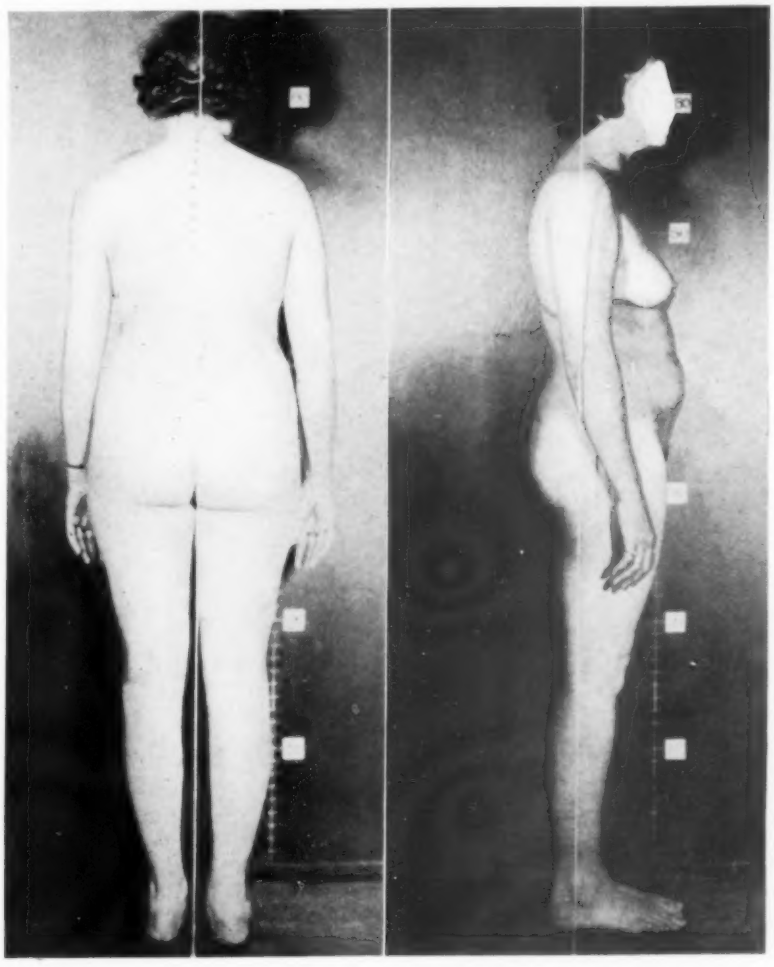

FIG. 4. Antero-posterior and lateral views of patient with pylorospasm of "viscerospinal" type. Note pelvic tilt producing lumbar scoliosis and secondary curves in dorsal area. Lumbar lordosis and compensatory kyphosis shown in lateral view. Correction made by right heel raise and postural exercises. Relief of pylorospasm complete and lasting.

motility and in the tone of the pyloric sphincter are produced in all probability by either.[35] Furthermore as clinicians we are particularly concerned with the effects produced by spinal curvatures, myositis, osteoarthritis, etc., in the mid dorsal and lower spine in relation to these viscera and not with the predominance of one or the other of the nerve groups. (Figures 4 and 5.)

Pylorospasm has been the chief objective finding, while nausea, a sense of epigastric fullness, gaseous eructation, colicky pain and vomiting have been most frequently noted by the patient. Usually some points of tenderness along the spinous processes or laterally in the mid-dorsal musculature

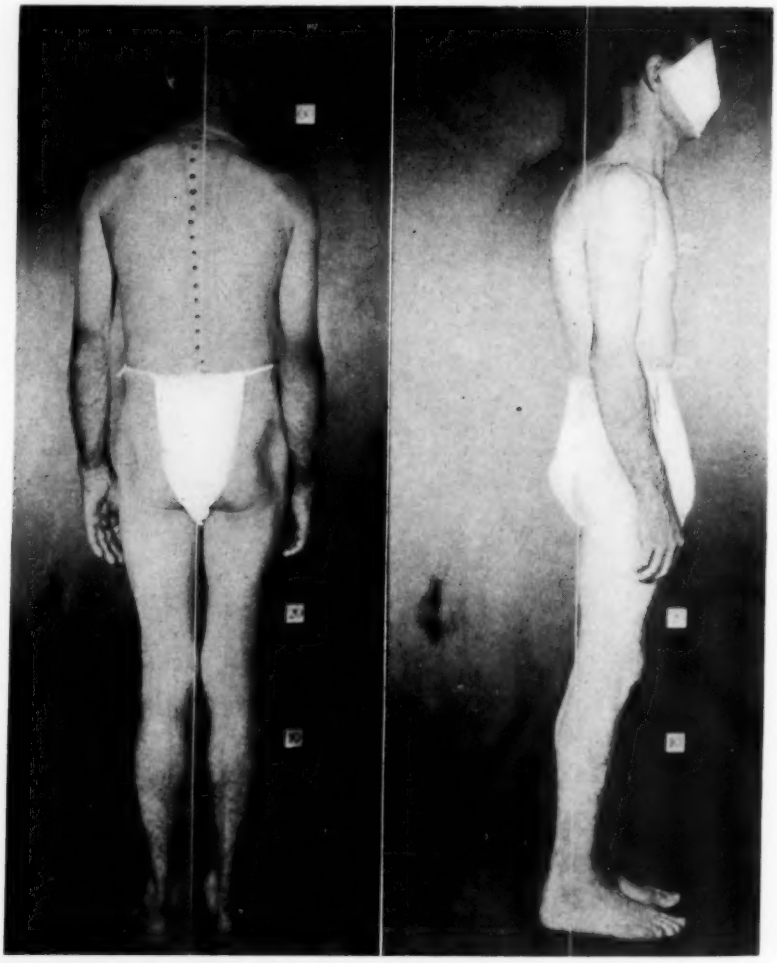

FIG. 5. Postural deformity related to pylorospasm. Corrected by exercises and resulting in relief of long standing symptoms.

have been found. Intercostal tenderness radiating from this point is common. The patient may associate his epigastric symptoms with pain between his scapulae. Hyperesthesia of the skin may be suggested by the complaints of clothing being especially irritating in this area. In many instances the previous treatment has consisted of ulcer management. Antispasmodics and sedatives have also been used particularly where marked pylorospasm was

present (Case 9). In general, results have been disappointing and the patient has made the usual medical rounds for relief.

When all other factors contributory to an ulcer history or pylorospasm were ruled out by roentgenograms or laboratory examinations the patient with the suspected viscerospinal disturbance was put on a therapeutic test. This consisted of a correction of the postural defect, of the articular irritation, or of the myositis related to the mid-dorsal area. Physiotherapy including local infra red irradiation and massage was used in some cases to speed up the mechanism of correction. If without medication the symptoms of pyloric obstruction or gastric irritation disappeared for a sufficient period the patient was considered with reservations a candidate for the viscerospinal classification. Further confirmation was often found in the return of symptoms on reformation of a dorsal scoliotic curve. This occurred in some instances, for example, as a result of not wearing a required heel raise or not maintaining an adequate postural regime. (Figure 4.) Still further proof was gathered in some cases in which local physiotherapy had repeatedly produced immediate yet not lasting relief of gastric symptoms and which subsequently obtained extended relief by orthopedic correction of the spinal irritation.

In some of the following case reports segmental distributions other than that of the stomach and pylorus were involved but the chief complaint was directed to the upper alimentary tract.

Case 9. Mrs. K. McC., a moderately obese woman of 38, telephone operator.

Family History: Father died of tuberculosis. Husband ill with same infection.

Past History: Usual childhood diseases. "Double pneumonia" 1919. Appendectomy and resection of left Fallopian tube 1925. Diagnosis of chronic salpingitis, 1932. Injection of external hemorrhoids, July 1934.

Present Illness: Gastrointestinal complaints were a feature during observation in the Santa Barbara Clinic for 14 years up to the time of my first examination in September 1934. (Patient previously was treated by four internists for "colitis," "pain in the right lower quadrant," "constipation," "sour stomach," "pylorospasm" and "peptic ulcer.") At this time her chief complaint was epigastric fullness and distress lasting some three to four hours after eating. She believed it was difficult for the food to pass out of the stomach and was awakened at night by the epigastric distress. Her symptoms were often accompanied by occipital headache. A rather stubborn spastic constipation was also present.

Laboratory: Repeated Wassermann and routine blood examinations were found to be negative. The stools were negative for occult or gross blood during observation over a period of 10 years. There were no urinary findings of note. Roentgen studies of the gastrointestinal tract in 1927 suggested a possibility of a prepyloric lesion provided "the clinical history and gastric analysis confirmed." Two additional series were studied in the interval between 1927 and 1934 outside the clinic and no evidence of peptic ulcer was found. In 1934 detailed roentgenological studies were again made by Dr. D. M. Clark at which time a marked pylorospasm was found which persisted for a considerable time after the ingestion of barium. There was no evidence of an ulcer niche or of any characteristic deformity. The gall-bladder was negative. A gastric analysis was refused by the patient at this time (although one analysis, according to the patient, done in Los Angeles in 1925, showed a low acid reading.

Examination: A rather well developed woman of 38, who appeared fatigued and in some distress. A refractive error was corrected by glasses. Her teeth showed moderate need for repair. Her lungs were clear. Her heart sounds were lacking in tone. The systolic blood pressure was 130, diastolic 80. On palpation of the abdomen some resistance was noted in the epigastrium and the patient complained of slight nausea. No masses or particular tenderness were noted. On examination of the back an antero-posterior and lateral angulation was noted in the region of the fourth and sixth dorsal spines. A fairly good correction of this lateral curve was obtained by a half inch lift on the left heel. The dorsal kyphosis apparently resulted as a compensation for her lumbar lordosis.

Treatment and Progress: Medication directed toward alleviating the gastric distress and pylorospasm was instituted from the beginning. Tincture of belladonna, barbiturate and alkaline powders were used for a period of six months. In addition a modified ulcer program was maintained. No mental or family maladjustment could be found, but several vacations were prescribed away from her local environment. These measures proved to be ineffective—in fact her symptoms were aggravated by walking or riding in a car. Some complaint of pain in the interscapular area prompted a further consideration of her postural defects and a heel lift was prescribed on the left. A definite decrease in the back pain followed and along with it an improvement in the gastrointestinal symptoms. However, she still awakened several times in the early morning with back pain and epigastric fullness. Bed boards and postural exercises by the orthopedic department were then recommended and the symptoms disappeared completely.

All medication was stopped but the exercises were continued. Up to the present writing more than a year has elapsed without a recurrence of gastric distress or pylorospasm. The constipation which was a fairly constant complaint is also gone.

The Small and Large Intestines. An arbitrary division of the alimentary canal is made here although an anatomical division of the nerve supply to the pyloric portion of the duodenum and the sigmoidal portion of the colon cannot be entirely divorced from the connecting intestinal tract. This is done for two reasons. In the first place the innervation of the small and large bowel is primarily from a lower segmental plane than is the innervation of the stomach, and from a higher plane than that of the sigmoid. In the second place a clinical division of the tract is necessary on the basis of symptomatology. By far the most frequent complaints noted in this study have been directly related to the intestinal tract. In my preliminary report I suggested that the terms "chronic appendicitis," "intestinal colic," "colitis" were sometimes wrongfully used by internists and surgeons alike when physiological changes in these viscera were due to extrinsic nerve irritation, and not due to pathological changes in the viscera themselves. It was shown that many operations for "chronic appendicitis" had been performed uselessly and without relief of symptoms when this vital point was insufficiently recognized. Carnett [8] had previously determined the results of a series of operations for chronic appendicitis done by a large group of capable surgeons and found that in a fairly high percentage, the patients were not relieved by the operation. He concluded that operative failure in many instances was due to the confusion existing in the mind of the operator between parietal pain (intercostal neuralgia) and pain caused by a pathological viscus

beneath. This was a good point as far as it went but I maintained that in addition to this somatic neuralgia radiating from the spine, actual changes in visceral function were produced by essentially the same mechanism. Colicky pain effected by the contraction of a hypertonic gut on imprisoned gas was shown to be related to spinal curvatures or associated myositis. Surgical confirmation of the syndrome was soon found when Wills and Atsatt [36] presented evidence of localized visceral irritation and spastic bowel paralysis following trauma of the lumbar muscles. They described several cases in which external or parietal neuralgias were accompanied by actual visceral changes.

The majority of patients that I have classified under this particular viscerospinal grouping have suffered no acute trauma to the related spinal structures. Usually they give a history of recurrent back pain in the lower dorsal or upper lumbar region. On examination angulation of the spine with or without demonstrable muscle rigidity is often present. A lumbar lordosis is probably the most frequent spinal curvature observed. Again as I have shown in the segments related to the lungs, heart, esophagus, etc., the correction of the postural defect has resulted in relief of the intestinal disturbances. Postural exercises, heel raises on the short side, supportive physiotherapy have all contributed to the result. At least 40 patients have been spared operations for "chronic appendicitis" in our own series due to the recognition of these radiation phenomena. Full coöperation of the surgical and orthopedic departments has made this possible.

Case 10. M. E. S., auto mechanic, aged 27, referred from the endocrine department of the clinic May 31, 1933.

Past History: The family and past histories were irrelevant except for attacks of "chronic appendicitis" for two years.

Present Illness: The patient complained of general discomfort in the right lower quadrant with slight transient pain when markedly constipated. The constipation was quite persistent and required cathartics once or twice a week in spite of dietary regulations and habit programs for several years. A numb feeling below the right shoulder was a recent complaint.

The patient was of the opinion that an operation for his "chronic appendicitis" would probably help his constipation.

Examination: A tall, well developed young man with a moderate exophthalmos and conjunctival redness. There was no evidence of disease of the heart or lungs. There was a slight hyperesthesia of the right lower abdomen as compared with the left. No muscle rigidity was noted. Examination of the back revealed a definite dorso-lumbar curve, antero-posterior as well as lateral. The right leg was one half inch short, producing a pelvic tilt to the right. Correction of this shortening produced a fair realignment of the dorso-lumbar spine and erased the angulation in this area.

Laboratory: The blood examination including the Wassermann reaction was negative, as was a single urine specimen. No stool specimen was examined.

Treatment and Progress: No medication was given, but a half-inch total right heel lift was prescribed for the dorso-lumbar curve. Within two weeks the subscapular numbness and the discomfort in the right lower abdomen disappeared. There was also a complete relief of his spastic constipation although no mention of such a possibility was made to the patient. During the following year the patient maintained his freedom from symptoms referable to the lower gastrointestinal tract.

Comment

Controlled observation of the complex extrinsic and intrinsic factors governing intestinal activity is difficult. The vagaries of neuroses, nervous tension, allergies, ulcers of the gastrointestinal tract, indigestion, and allied factors must all be considered in relation to the viscerospinal syndrome.[37] Roentgenograms may or may not be of value. Placebos and unrelated therapy must be used to rule out psychic elements. Weiss' technic[33] of injecting the cutaneous area of maximum pain with a local anesthetic has also been used with good effect in making the distinction between actual and imaginary abdominal distress. Subjective complaints of bloating and fairly well localized gaseous distention are quite important provided an adequate control is maintained. Added confirmation of the syndrome is offered when relief is obtained by such a measure as simple postural correction without local physical therapy.

The Sigmoid and Rectum. Spasm of the rectal sphincter or inhibition of the musculature of the sigmoid and rectum producing constipation are the chief functional disturbances involved here.

To summarize briefly the nervous pathways it must be remembered that three divisions of the anal canal are to be considered: (1) the lower portion of the sigmoid; (2) the internal sphincter; and (3) the external sphincter and its muscle group. The latter is primarily under voluntary control. The internal sphincter is supplied by the sympathetic and parasympathetic nerves as is the sigmoid and descending portion of the colon. Without going into the neuro-anatomy in detail it may be stated that the hypogastric and pelvic plexuses which supply the sigmoid and anal canal receive autonomic fibers from rami related to the lower lumbar and sacral segments.

Theoretically, in common with the upper segmental areas, irritation of the peripheral afferent sympathetic fibers due to lower lumbar myositis, articular dysfunction, or tortipelvis produces definite disturbances in rectal elimination. Constipation should be the most common finding, as expulsive power cannot be voluntarily controlled by the inner sphincter even though the external sphincter can adequately relax. Conversely excessive peristalsis with its expulsive action in the sigmoid region due to extrinsic nerve irritation is automatically controlled by the voluntary tonus of the external sphincter even though the inner sphincter be completely relaxed.

These theoretical considerations have been borne out repeatedly by clinical observations. Spastic constipation associated with low lumbar irritability has been shown to disappear after correction of one or more derangements of the lower lumbar or sacral areas (figure 6). Very often a pelvic tilt due to a short leg or actual asymmetry of the pelvic girdle can be remedied by a heel lift on the short side. This simple procedure without application of other therapy has produced lasting relief of intractable constipation in a considerable number of cases. (The word 'intractable' is used to denote those cases where roughage, fruit juices, mineral oils, habit training, seda-

tives, etc., have been used with little or no benefit.) The lumbar region is the site of most primary curves [18] and it is not strange that this should produce visceromotor changes as well as the numerous low back pains of the external parietal type (Cases 2, 8, 9 and 10).

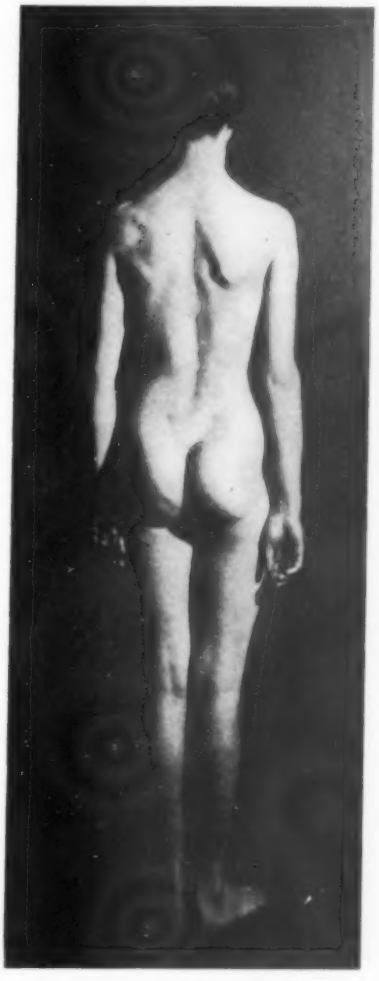

FIG. 6. Typical postural deformity in lumbar and lower dorsal area related to lateral pelvic tilt. Genito-urinary disorders and spastic constipation on viscerospinal basis often seen in this type of case. Lighting of figure from one side aids in visualizing abnormalities of skeletal structures.

GENITO-URINARY TRACT

In my preliminary report I presented cases in which the viscerospinal syndrome was shown to involve the genito-urinary tract. No detailed description of these cases was given, nor did I attempt to explain the probable physiology. Wills and Atsatt [36] in 1934 offered further substantiating evi-

dence by reporting two patients, one of them (Case 12), in whom ureteral spasm was relieved after postural correction. Complete urological examinations with repeated bougie dilatation of the ureters had proved of little benefit until the extrinsic irritation of the spinal area was removed. This was done along the usual orthopedic lines.

Clinical studies of the urinary tract with the syndrome in mind have been restricted chiefly to ureteral spasm and urinary frequency. Thus far detailed study of renal function or changes in urinary components has not been carried out to a satisfactory conclusion. However, as will be shown, the diuresis of the kidney proper as influenced by the autonomic system may have a direct bearing on the urinary frequency.

To understand the physiological changes involved in the syndrome we must again summarize the autonomic nerve pathways to the kidneys, the ureter and the urinary bladder.

The Kidneys. A thick network of sympathetic fibers to the kidney is traced through the major splanchnics and communicating branches from the lesser splanchnics. Vagus (parasympathetic) branches run directly to the renal plexus in most instances passing through the coeliac ganglia. The consensus suggests that the sympathetics govern the urinary output of the kidney principally through vasoconstriction or dilatation of the renal blood vessels.[7] Interesting conjectures arise as to how external somatic factors may influence the renal output. Clinical observations in the past have suggested that exposure with chilling of the lumbar region may be followed by a suppression of kidney output and conversely that hot packs to this region may sometimes stimulate diuresis. If it should prove that a small fraction of renal disorders are due to reflex effects of the viscerospinal type we should be well repaid for the attempt to draw attention to this mechanism.

The Ureter. Peristaltic waves in the ureters are probably due to both intrinsic and extrinsic excitation of the thick ureteral musculature.[7] That this peristaltic wave can be so violent as to produce pain is not to be doubted, particularly when a distal portion of the tube is partially blocked. The chief question here arises, however, as to the effect of extrinsic autonomic stimulation in producing the colic. Hryntschak [41] in 1925 corroborated Engelmann's [42] earlier findings that the ureter requires neither intrinsic ganglion cells nor extrinsic nerves for its functional regulation. Kuntz [7] on the other hand is of the opinion that the abundant nerve supply to the ureter cannot be devoid of functional significance. He suggests that "maintenance of the tonus of the ureteral musculature and reflex coördination of the activities of the ureter to contractions of the bladder probably represent the most important functions of the nerves supplying the ureter."

In our series symptoms of ureteral colic, ranging from mild ache in the flank to an extremely severe pain of intermittent type, have been present. How often the antiperistaltic action of a contracting and irritable bladder contributed to the symptomatology is not clear. Ureteral dilatation was found to be of temporary benefit in some instances, but lasting relief was

noted only after a thoraco-lumbar curvature of the spine, or a myositis involving this area was eliminated (Cases 11 and 12).

The best substantiation of the viscerospinal syndrome in relation to the symptoms of ureteral spasm or 'stricture' must come from the urologist. A case studied and reported by Wills is presented.

Case 11. Mrs. J. H. P., white, married, 38 years old. She was first seen at the clinic in March 1935.

Family History: Father died of a stroke. Mother had "ulcers of stomach." One sister suffered at times from asthma.

Marital History: Husband and one child living and well.

Past History: Patient had most of the childhood diseases; and tonsillitis and influenza as an adult. A suspension of her uterus was done for lower abdominal pain in 1921. In 1923 during her only pregnancy she developed acute gastric and upper abdominal distress. She was thought to have an intestinal obstruction but no confirmation of this was obtained. In 1925 she fell and injured her "lower spine" which resulted in frequent lumbar pain for some time thereafter. Frequent occipital headaches were a feature of her adult life.

Present Illness: The patient's chief complaint on admission was marked distress in the stomach region with occasional nausea. Her symptoms were thought to be worse following meals. She also complained of frequency and of pain radiating down her right posterior thigh. She noted an increase in frequency and also some burning on micturition after being on her feet for several hours. (The latter symptoms had previously been noted under similar circumstances in 1933.) She was moderately constipated. There was a gain of 30 pounds in weight during the past year. She attributed many of her recent symptoms to weakness after an attack of influenza four months prior to this examination.

Physical Examination: The patient appeared to be in good health and younger than her recorded age. She was well developed and moderately obese. Her skin was moist and gave evidence of some vasomotor imbalance. Her heart was slightly enlarged to the left. The systolic blood pressure was 110, diastolic 80. The lungs were negative. The abdomen was protuberant and an old lower midline scar was present. No tenderness or hyperesthesia was noted on palpation. Pelvic examination revealed a large, moderately lacerated cervix. The uterus was in the anterior position and pulled to the left. No particular tenderness was elicited by the exploration. On examining the back, areas of tenderness were noted about the third and fourth dorsal spines. A lumbar antero-posterior and lateral curve was found in conjunction with a pelvic tilt to the right. (The latter was apparently due to a shortness of the right leg.)

Laboratory: Roentgenographic visualization of the gall-bladder indicated normal function. No stones were visible. (A gastrointestinal series made in Ventura, Calif. a few weeks before was reported to be negative.) Routine blood and urine studies were negative.

Treatment and Progress: A program of weight reduction coincidental with postural correction was instituted and a right heel lift was prescribed. Less epigastric distress and "heart burn" was noted within two weeks although some pain persisted in the right hypochondrium for approximately four weeks. The urinary frequency and burning disappeared, however. The patient's condition improved thereafter. She remained free of her symptoms up to April 1936 when her heel lift was not worn for a period of six days. Return to the correction resulted in prompt relief of symptoms.

Case 12. A white truck driver, married, aged 26, was referred to us complaining of intermittent pain in the left flank radiating to the back and lower part of the

abdomen. The patient stated that the pain was always worse after he walked or rode in a truck. Usually he felt well on rising, but the pain came on increasingly as the day wore on. Nausea occurred frequently during attacks of pain. He had lost 20 pounds (9.1 kg.). The duration of the condition was two and one-half years in which he had made the rounds of physicians and cultists with no relief.

Examination: The examination revealed tenderness high in the left lumbar region and in the lower left quadrant of the abdomen on deep pressure. The abdominal muscles were slightly rigid. The left kidney was not palpable. A cystoscopic examination showed that the mucosa of the bladder was normal. The left ureter was catheterized with difficulty, using a number 4 (French) catheter. The urine gave negative results culturally. No evidence of tuberculosis was seen, and inoculation of guinea pigs gave negative results. Pyelograms showed the kidney to be in normal position; no abnormality was seen. Filling of the renal pelvis reproduced the pain (voluntary statement) but more severe than ordinarily. A diagnosis of stricture of the ureter was made.

Treatment: Dilation of the left ureter at first gave relief for a day or so; later these treatments were of no benefit even after dilation with a number 12 catheter. On reëxamination a number 5 catheter was used and met with resistance. Attempts to withdraw it revealed that it was in the grip of a spastic ureter.

The patient was referred to the orthopedic department. Here was found a spastic left dorso-lumbar region with tenderness of the muscles on pressure and a short left leg. There was a moderate scoliosis. The heel was raised one-fourth inch (0.64 cm.), and muscle training was given. The pain left within a few hours and within two weeks the patient could walk several miles without discomfort. The appetite returned and the patient regained five pounds (2.3 kg.) in the first month. Two and one-half months later he was working and free from pain. The only recurrence he has had took place one day when he wore his old shoes on which there was no heel correction.

The Urinary Bladder. As does the sigmoid and rectum, the urinary bladder derives its extrinsic nerve supply from the hypogastric (sympathetic) and pelvic (parasympathetic) nerves. This innervation as in many other segmental areas is mutually antagonistic. In general sympathetic stimulation results in inhibition of function whereas the result of parasympathetic stimulation is functional activity of the organ. It is also probable that inhibition of one of the antagonistic nerve groups results in increased effectiveness of the other.

Clinically the same external somatic factors (lumbar myositis, lumbosacral derangements of articulation, etc.) that induce tonic obstipation in the rectum are also of importance in producing motor and sensory disturbances of bladder function. Urinary frequency and urgency, for example, have been noted in many of our cases where lumbosacral irritation was present. Relaxation of the lumbar muscles through physiotherapy or correction of a pelvic tilt has resulted in complete relief of symptoms. (Figure 6.) It is difficult to evaluate the respective rôles of the kidney, ureter and bladder in regard to frequency. In any case the postulates of the syndrome apply to these individually or collectively as shown above. Presumably, on this basis, increased diuresis through the kidney, increased peristaltic action of the ureter, and increased tonic contraction of the urinary bladder acting either singly or together may produce frequency.

General Discussion

In reviewing the case reports as a whole and the segmental areas individually there are several points in discussion that are common to the various divisions involved. I have already suggested three points of excitation in or near the spine that act separately or in unison through well defined nerve pathways to produce physiopathological changes in the viscera. I have attempted to demonstrate that these points of stimulation in the skin, the dorsal musculature, and the vertebral articulations (figure 1) may be eliminated or markedly reduced in activity by postural correction and by local physiotherapy. . The result of such procedures has been to relieve the patient of symptoms associated with deranged physiological activity in the related segmental areas of the body. To simplify and correlate the various factors in the above relationship in contradistinction to the usual coexistent peripheral radiation phenomena I have suggested the term "viscerospinal syndrome." This term presupposes that the peripheral and the visceral components of this syndrome may be studied in one or all of the segmental areas. This is borne out by the above studies in spite of the arbitrary grouping of the segments for convenience of description.

In general the type of excitation may be the same at different levels of the vertebral column but the response in the visceral portion of the nerve distribution is entirely dependent upon the characteristics of the viscus involved. In other words ureteral spasm on the viscerospinal basis may be produced by a myositis of the dorsal musculature (Case 12). Bronchoconstriction may be a result of a similar myositis at a higher level (Cases 3, 4, 5, 6). Ureteral colic on the one hand and asthma on the other are thus related in their pathogenesis but naturally they differ in symptomatology.

It is evident from these studies that the viscerospinal syndrome is consistent in its manifestations within the range of physiological differences found at different spinal levels. It is not so clear, however, as to the exact rôle of the sympathetic as against the parasympathetic in the production of the syndrome. It is beyond the clinical scope of this paper to determine, for example, whether overstimulation of the sympathetic fibers brings about a pylorospasm of the viscerospinal type or whether the effect is produced by inhibition of the vagus impulses to the pyloric area. Alvarez[43] has shown in experiments on the rabbit that if intestinal muscle is stimulated while it is in a state of high tone, it may relax, but if stimulated when it is relaxed contraction is likely to result. In man the sympathetic-parasympathetic antagonism described by the physiologists is an imponderable factor when clinical studies such as these are made.

To prove that the points of irritation (cutaneous, muscular or articular) near the spine are primarily stimulating to post-ganglionic fibers supplying the viscus would require more physiological research than is feasible here. It may be that physiopathologic changes in these spinal structures actually produce an inhibition of sympathetic impulses. In turn this inhibition may

allow parasympathetic tone to predominate, resulting in what appears to be an actual parasympathetic rather than sympathetic action on the viscera.

Whatever the correct interpretation of the mode of action may be it is probable that profound physiological changes in the viscera can be demonstrated along the disturbed segmental nerve distributions. Furthermore it is suggested from a study of these cases that continued physiological disturbances may produce definite pathological changes as end-results.

A number of criticisms have been offered by clinicians as to the possible implications of the syndrome. The actual nervous pathways involved were not understood by some. Others denied the postulate of external somatic changes as being related to internal visceral disturbances except through humoral physiology. It has been shown, however, by neuro-anatomists and physiologists that the nerve pathways are present. It has also been shown by the mere mechanical correction of posture—through a heel lift, for example—that an articular defect of the spine may be eliminated and along with it the related visceral disturbance (Cases 1, 10). This would tend to rule out a humoral mechanism.

Following my preliminary report in which I stressed the rôle of spinal curvatures in relation to visceral disturbances the following questions were most frequently asked. "Many people have spinal curvatures and yet do not suffer from visceral disease. Why is the syndrome present in one and not in another?" This is a reasonable question and I believe can best be answered by the orthopedists who are conversant with the external radiation phenomena of radiculitis and intercostal neuritis related to spinal curvatures. Atsatt [18] explains this point as follows: "The neurological complications of scoliosis are governed largely by fatigue and come as the result of lowered skeletal resistance. The forces of gravity continuing to act over a long period of time gradually increase the off center curves, increase the muscle fatigue and irritation and thus give rise to nerve stimulation." He states that "Some incident such as long bed rest, unusual fatigue or strain with muscle atony and atrophy may act as the point of climax to initiate the neurological chain of events."

In untreated cases a history is given of frequent periods during which the patient is free or practically free of his radiation disturbances. The question is asked, naturally enough, "Why should the pain disappear when the scoliosis remains as a focus of irritation?" This again may be answered by the orthopedists who recognize the fact that "intercostal neuritis" may be a recurrent symptom of scoliosis characterized by frequent and often long standing remissions. They explain the vagaries of neuritis, on the basis of changes in muscle tone and fatigue which aggravate a scoliosis and set up articular or muscle irritations. These in turn produce nerve radiation phenomena. It is the *acute* irritation that produces symptoms and not the fixed and stabilized spinal curvature such as found in Pott's disease or in the patient with the congenital hip.

Other factors which are noted in common with the parietal disturbance of the intercostal neuritis type should be discussed at this point. It has been observed that climatic changes of an indefinite nature i.e., from the summer to the fall months or from winter to spring, as well as changes from dry to rainy weather or vice versa, are conducive to attacks in many patients suffering from radiation pain. The visceral component seems to go hand in hand with the peripheral symptomatology in many instances. Interscapular pain, for example, may be accompanied by gaseous distention of the upper abdomen and with epigastric colic. The patient claims in many instances that pain develops when it is " building up for a rain " and is relieved shortly after the rain has fallen. I have no explanation for this but offer the observations for what they are worth. In many cases the symptoms are brought on sharply during the late afternoon as the warmth of the day diminishes. Patients who suffer from the syndrome hesitate to allow themselves to be chilled. They find heat applied to the area of back pain to be of benefit long before such therapy is suggested by the physician.

Still another criticism is directed toward the interpretation of the benefits derived from the mechanical correction involved in these cases. This criticism assumes that the benefits are purely psychic; that something is 'being done' for the patient; that the patient's general health, and therefore his mental state, is improved by a betterment in postural tone. I readily admit that the psychic element is one of the most difficult factors to evaluate in clinical research and that experimental work is often rendered worthless by insufficient consideration of this important element. However, I have little patience with the constant application of the term " psychic benefit " to refute the claims made by clinical investigators in the autonomic field. Undoubtedly the mental state influences the sympathetic and parasympathetic balance in many of the patients studied. It is also true that psychotherapy and sedation have aided in the recovery of patients with visceromotor symptoms. But these factors have been repeatedly eliminated as being of minor importance in a given case once the viscerospinal syndrome is definitely established. In questionable instances local anesthesia of the related cutaneous areas according to the technic of Weiss and Davis [33] has been used to rule out the psychalgias. Preliminary sedation as well as placebos have also been used in making the differential diagnosis and in directing the patient's attention away from the real therapeutic procedures. As a matter of fact the difficulty has often been to persuade the patient that such a small item as a heel correction, or simple exercises for a scoliosis has any connection with his cure. Many times a placebo has been used to keep a patient satisfied and to insure his return for observation because of his skepticism in regard to his " unrelated " treatment. I believe that patients in this group are the least liable to be benefited because of subjective considerations. Their typical reaction is expressed by the common question, " Doctor, why do you pay so much attention to my back, when it's my stomach that is hurting me? "

In closing may I reiterate the necessity for recognizing the importance of physiology in relation to clinical problems. Viewing disease from the pathological approach is often a confession of failure to recognize the early physiological changes. Surgery, for example, has taken the lead in a field of physiology which should rightfully belong to the internist. The essential hypertensive, long considered a pet of the internist, is referred to the surgeon for splanchnic section. To relieve the patient with cardiac pain it is the surgeon who is asked to inject the upper thoracic ganglia. Raynaud's disease is often given up as intractable by the internist and sympathectomies are performed. But with all his success the surgeon admits he is merely severing efferent or afferent pathways which act as simple conduits for physiological impulses. He is not attacking the basic condition which primarily initiates these impulses. There is a derangement yet more remote than the ganglionic fibers involved in the cardiospasm or the hypertonicity of the intestinal tract. In cases presenting the viscerospinal syndrome the basic stimulus (or inhibition) is superficial to the cord and consists of afferent impulses. From our studies an important etiological factor is the somatic triad: Skin, dorsal musculature or vertebral articulations (figure 1). By correcting disturbances in this triad we may find at least one substitute for the hitherto necessary attack by the surgeon on the visceral nerve pathways anterior to the spine. Here we are dealing with causes rather than with end results of autonomic nerve disorders.

The body must be integrated as a whole. It must function as a whole adapting itself to external as well as internal stimuli. For some time the clinician has been so engrossed in the effects of visceral dysfunctions and their *outward* manifestations that he has neglected the skeletal structures with their disturbance reflected *inward* on the viscera. The syndrome herein described emphasizes the latter phase of physiological balance.

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CALCAREOUS AORTIC STENOSIS; REPORT OF NINE CASES WITH AUTOPSY FINDINGS *

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Calcareous aortic stenosis, or stenosis of the aortic valve with calcification of the cusps, is a clinical entity which is receiving increasing attention. Probably the most important clinical feature has been, and remains, the disproportion between the clinical signs and symptoms during life as compared with the marked changes present in postmortem examination. Patients suffering from aortic stenosis have a clinical course which is entirely distinctive from that of either mitral disease or mitral and aortic disease combined. On analyzing the age incidence, the physical signs, the age at which symptoms first appear and the mode of death, it becomes quite evident that patients with calcareous aortic stenosis comprise a well segregated and defined group. A rather distinctive and characteristic finding in this group is the paucity of symptoms directing attention to the heart until the abrupt onset of cardiac manifestations.

Literature

Trousseau[1] was among the earliest clinicians to recognize the peculiarities associated with aortic valve disease. He called attention to the occurrence of sudden death in lesions of this valve and " the absence of the assemblage of the phenomena which constitute the general symptoms of disease of the heart." In 1892, Vaquez,[2] with his teacher Potain, examined a woman, 60 years of age, who had a murmur of aortic stenosis. Some 20 years later he again saw her on her death bed, and learned that in the interval of 20 years she had been very comfortable.

Osler[3] borrowed a phrase from Oliver Wendel Holmes when he expressed the thought that this lesion is not only compatible with continued good health, but that "it may promote longevity." Following Osler's discussion in 1888, contributions by Cabot,[4] Moenckeberg,[5] Christian,[6] Clawson and his co-workers,[7] Hathaway,[8] Libman,[9] and more recently Margolis and his co-workers,[10] McGinn and White,[11] and others have added a great deal to the present knowledge of calcareous aortic stenosis.

In this communication we are reporting nine cases of this clinical entity with a summary of the essential findings of the cardiovascular system as noted at autopsy. All of our cases but one were males. The ages ranged between 46 years and 84 years.

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Case Reports

Case 1. A. K., a male adult, aged 72 years, was admitted to the hospital on April 23, 1935, complaining of dyspnea and orthopnea of two months' duration. The family history and the past history were essentially negative. The present illness dated to some eight weeks before admission when the patient first began to complain of shortness of breath on exertion and the necessity of sleeping "sitting up in bed." Prior to admission to the hospital he had been under digitalis therapy and had occasional precordial pain lasting for a few minutes at a time The essential findings on physical examination were dyspnea, orthopnea and cyanosis in a well preserved, white, male adult. The heart was enlarged to the left, the rhythm was regular, and the sounds were of poor quality. At the lower end of the sternum and somewhat to the left, a saw-rasping systolic murmur was heard. Over the aortic area a rough systolic murmur was heard which radiated upward into the vessels of the neck. The second aortic sound was not audible. Râles were heard at the right base, and the liver extended some 6 cm. below the costal border. There was no peripheral edema. The systolic blood pressure was 100 mm. of mercury and the diastolic 48 mm., and the pulse rate was 60 per minute. Serology was negative. Blood chemistry findings were normal. There was increasing dyspnea and orthopnea. The patient died 12 hours after admission to the hospital.

Autopsy Protocol. The heart weighed 580 grams and was markedly hypertrophied and dilated. The wall of the left ventricle measured 2 cm. in thickness, that of the right 0.5 cm. in thickness. All the chambers of the heart were markedly dilated and contained postmortem clots. The tricuspid valves were slightly thickened and opaque. The chordae tendineae were slightly hypertrophied. A probe, passed from the left ventricle into the aorta, met with marked obstruction and was admitted into the aorta only with difficulty. The semilunar aortic valves were thickened, markedly sclerosed and calcified. The edge of one of the cusps measured 0.5 cm. in thickness and was markedly calcified. The pulmonary valves were slightly sclerosed. The coronary arteries were pipe-stem in nature, markedly sclerosed and easily traced throughout their entire course. There was no recent obstruction. The aorta showed marked atheromatosis, calcareous deposits and ulcerations.

Comment. This 72-year-old man was clinically well until two months prior to his death. Following the onset of symptoms of heart failure there was a rapid and progressive downhill course. The important findings on examination of the heart were the rough systolic murmurs heard over the aortic area and in the region of the mitral valve, and an inaudible second aortic sound. At autopsy the aortic valves were found to be thick, sclerosed and calcified.

Case 2. S. G., a white male adult of 46 years of age, was first admitted to the hospital on April 8, 1935, complaining of a cough of many years' duration and shortness of breath of one month's duration. The patient's mother had died of "heart trouble" but there was no other family history of cardiovascular disease. The past history revealed the fact that at the age of 12 he had had malaria, at 18 had a nephropexy, at 30 had gonorrhea, and at 39 had pneumonia and pleurisy. There was also a past history of frequent upper respiratory infections. One year prior to admission to the hospital he had been having increasing shortness of breath on exertion and for the past month had had attacks of nocturnal dyspnea and palpitation. The essential findings on examination were dyspnea and orthopnea, enlargement of the heart to the left, presence of a presystolic murmur at the apex, and a rough systolic murmur over the aortic area, transmitted upward to the vessels of the neck. The second aortic

sound was not heard. A thrill was felt over the aortic area. The peripheral blood vessels were thickened and the pulse was small. Cardiac rate was rapid, rhythm was regular and the muscle tone was of fairly good quality. There was evidence of right and left hydrothorax and the liver was enlarged two fingers-breadth below the costal border. No sacral or pretibial edema. Roentgen-ray examination showed an enlargement of the heart, predominantly left ventricular, with increased vascularity throughout the pulmonary parenchyma and effusion in both chests. Fluoroscopic examination, with the administration of barium outlining the esophagus, revealed a left auricular bulge and enlargement of the left ventricle. Electrocardiographic studies showed: Lead I, regular sinus rhythm, slurring of R and negative T. Lead II, negative P, slurred R, depressed ST and diphasic T. Lead III, negative P, slurred and notched QRS. Interpretation: Left axis deviation, severe myocardial disease and auricular involvement. The blood pressure varied from 140 to 118 systolic and from 84 to 60 diastolic. Blood chemistry findings were normal, and examination of the urine showed a trace of albumin and a few granular casts. Following the continuance of bed rest, low caloric diet and digitalis therapy, signs of congestive heart failure gradually decreased and the renal findings returned to normal. The pleural effusion disappeared, the patient's condition improved, and he was discharged on April 23, 1935, 15 days after admission. The diagnosis at this time was: arteriosclerotic heart disease with calcareous aortic stenosis, calcification of the mitral ring, left and right heart failure and bilateral hydrothorax. Four days after discharge from the hospital the patient was readmitted with a history of having experienced a very severe attack of pain in the epigastrium several hours previously. The pain continued, radiated to both axillae and shoulders, and the patient "felt as if dying." Examination showed the patient to be dyspneic and cyanotic; the heart sounds were weak and rapid and the skin cold and clammy. Blood pressure on admission was 128 systolic and 60 diastolic and within a few hours dropped to 98 systolic and 64 diastolic. The murmurs heard and described on the first admission were present but less intense in character. Within 24 hours the temperature was elevated to 102° F. A pericardial friction rub was heard over the lower end of the sternum. Electrocardiographic study at this time showed changes indicative of progressive myocardial damage as compared with the tracing taken some three weeks previously, but no characteristic changes to indicate a recent coronary occlusion. His condition remained critical. Eight days after admission he suddenly became markedly dyspneic and cyanotic. The pulse was rapid and feeble and the blood pressure was so low it could not be estimated. The chest was full of râles, and the patient expired within a few minutes after the onset of this attack.

Autopsy Protocol. The heart and aorta weighed 500 grams and lay free in the pericardial sac. On the anterior surface of the left ventricle, close to the apex, there was a small circumscribed patch of fresh fibrin. The left ventricle was hypertrophied and there was very little dilatation present. The aortic valve was rigid and fixed and the leaflets were replaced by firm bone-like masses. The anterior descending branch of the left coronary artery presented in its lumen a fresh adherent thrombus about one and one half centimeters from its termination. The myocardium in this vicinity showed hemorrhagic infarct.

Comment. The marked calcification of the aortic valves, as noted in the autopsy, undoubtedly existed many years before the onset of the clinical symptoms of heart disease which were first manifested two years prior to death. The anginal syndrome, we believe, was due to the coronary artery disease. This man was the youngest of those included in this group. The classical attacks of left ventricular failure were followed by coronary artery thrombosis which necessitated re-hospitalization. The physical examination

revealed criteria which we believe are confined to those who have calcareous aortic stenosis, namely a rough systolic murmur over the aortic area transmitted to the vessels of the neck, absent aortic second sound, palpable thrill over the aortic area and small pulse.

Case 3. N. W., a male adult 66 years of age, was admitted on April 10, 1934, with a history of five previous attacks of precordial pain and shortness of breath during the preceding six months. His immediate condition, necessitating hospitalization, was of 12 hours' duration, and was manifested by precordial pain, vice-like in character, and by dyspnea and cyanosis. The essential findings on physical examination were the marked cyanosis of the lips, ears and finger-tips, pulmonary edema, systolic murmur and thrill over the aortic area, and a decrease in aortic second sound. An electrocardiogram taken at this time revealed left axis deviation and severe myocardial damage. Response to treatment for the attack of left ventricular failure by sedation, bed rest and digitalis therapy was satisfactory. The patient improved and was discharged from the hospital four weeks after admission. He was comparatively well for some 22 months when he was readmitted to the hospital (February 27, 1936), with a history of increasing dyspnea and precordial discomfort. These symptoms had appeared approximately a week prior to admission and were initiated by an attack of breathlessness which woke him from his sleep during the night. On examination there were all the evidences of left ventricular failure (numerous râles throughout both lung fields, marked pallor and cyanosis of the finger-nails and dyspnea). The essential findings on examination at this time were: the high-pitched musical murmur heard at the apex and transmitted upward to the aortic region where it was accentuated, absence of the aortic second sound, and enlargement of the liver (two fingers-breadth below the costal border). The systolic blood pressure was 210 and the diastolic 100 mm. Treatment by dry phlebotomy and sedation brought about definite relief of orthopnea, and the moisture in the lungs disappeared. An electrocardiographic study showed marked left axis deviation with progression of the severe myocardial damage, as compared with the electrocardiographic study taken in 1934. Some 24 hours after admission, when the patient was having his breakfast, he suddenly fell over dead.

Autopsy Protocol. The heart and aorta weighed 600 grams. The left ventricle measured 1.3 cm. in thickness and there was flattening of the musculature. The aortic valve showed marked calcification and the mitral valve revealed thickening of the cusps but no calcification. The intima of the aorta was brittle and calcified. The coronary orifices and vessels were patent throughout and revealed no evidence of old or recent thrombosis.

Comment. The postmortem examination of the heart failed to indicate any evidence to explain this rather sudden and unexpected death. The possible mechanisms responsible for the sudden death are discussed later.

Case 4. W. C., a white male adult, 80 years of age, was first admitted to the hospital, February 18, 1936. For three years prior to admission he had been complaining of "pain over the heart and in the back, with shortness of breath, getting worse in the last three months, and swelling of the legs for one month." He was able to carry on his work until some two (2) months prior to admission when, because of breathlessness and pain over the heart, he had to discontinue all activity. In recent months he was compelled to sit upright in order to sleep. On the evening of admission to the hospital he complained of "sharp pain over the heart with loss of breath." The essential findings on physical examination were the enlargement of the heart (apex beat in the sixth interspace at the anterior axillary line), a sharp, rasping, high-pitched

murmur at the apex, replacing the first sound, intensification of this systolic murmur at the aortic area, diminished aortic second sound and systolic thrill over the aortic region. Moist râles were heard at both bases. The liver was slightly enlarged and tender, and there was a slight pretibial edema. Blood pressure 140 systolic, 100 diastolic. The diagnosis of calcareous aortic stenosis with extension of the calcification downward to the mitral valve was made. After several days the patient left the hospital against advice, only to return three months later with marked dyspnea, orthopnea and precordial distress, palpitation and moderate edema of both legs. He presented the signs of congestive heart failure. On examination of the heart, the rasping murmurs previously described were heard over the mitral and aortic areas. Electrocardiographic studies done on three occasions showed auricular fibrillation with left bundle branch block. The patient failed to respond to treatment and died one month after admission to the hospital.

Autopsy Protocol. The heart weighed 700 grams and showed predominant enlargement of the left ventricle. Externally over the left ventricle there was a medium-sized, white, calcified, adherent plaque. On section the left auricle was average in thickness and the mitral valve leaflets were markedly calcified. The mitral orifice admitted one and one-half fingers. The left ventricle was markedly hypertrophied. The aortic valve leaflets were extensively calcified and opaque. The coronary arteries showed extensive calcification and sclerosis throughout, but there were no occlusions. The aorta showed marked atherosclerosis and calcified areas throughout. There was an aneurysm present in the hepatic artery, close to its origin, which was 1.5 cm. in diameter and filled with an old laminated blood clot. The spleen weighed 200 grams, was slate blue, and showed areas of old infarction. The kidneys showed old wedge-shaped areas of scar tissue.

Comment. The finding of a healed aneurysm of the hepatic artery and the presence of the infarcts in the spleen and kidneys naturally raise the question as to whether or not this man at some time previously had had a subacute bacterial endocarditis which had healed.

Case 5. P. G., a white male adult, 55 years of age, was admitted to the hospital in coma, on November 14, 1933, and died within a few hours. The history obtained from a relative indicated that the patient had had a known hypertension for three years, and that three weeks prior to admission he had sustained an injury to the left index finger. There was no history of symptoms suggestive of progressive heart failure. The "patient collapsed and went into coma" and was brought to the hospital. The physical examination revealed a comatose white male adult with extreme cyanosis. The heart was enlarged, rate increased, and rhythm regular. A loud rough systolic murmur was heard over the apex and the aortic area. The aortic second sound was distinctly less prominent than the pulmonic second sound. The lungs were clear; the liver was enlarged to two fingers' breadth below the costal border. There was no edema of the sacrum or of the tibia. There was an infection of the left index finger with pus exuding from several incisions. In view of the comatose state, spinal tap was done and the fluid returned was bloody but under normal pressure. There was no sugar present in the urine.

Autopsy Protocol. Examination of the brain revealed the fourth ventricle to be distended by a blood clot. On serial section, this blood clot extended throughout the entire fourth ventricle and seeped into the central canal of the cord, and the pons showed several hemorrhages throughout its length. There was no evidence of congenital aneurysm of the cerebral vessels. The heart weighed 800 grams. The lumen of the right ventricle was encroached upon by the bulging of the septum inward. The mitral orifice admitted two fingers. The valve leaflets were transparent and shiny.

The lumen of the left ventricle was of average size and the musculae carneae were rounded. The wall of the ventricle measured 1.8 cm. and was of a homogeneous brick-red color. The aortic valve had a bicuspid arrangement. The leaflets were shortened and the edges were somewhat rounded and calcified. The coronary orifices were widely open and the branches of both the right and left coronary arteries showed a moderate arteriosclerotic process. There was no sclerosis of any of the vessels, nor was there a recent thrombosis. The aorta showed a moderate atheromatous process without calcification.

Comment. Death in this case was due to extensive hemorrhage into the fourth ventricle of the brain. To the best of our knowledge there were no symptoms associated with the cardiac abnormalities as noted in postmortem examination. At autopsy a congenital bicuspid aortic valve was found with extensive calcification of the ring and leaflets. Examination of the cerebral blood vessels did not disclose any congenital or mycotic aneurysm.

Case 6. S. F., a white male adult, 47 years of age, was admitted to the hospital on October 15, 1936, and died within a few hours after admission. He had been well until midnight prior to the day of admission when he suddenly developed dyspnea and orthopnea. On admission to the hospital he was markedly cyanotic and expectorating a frothy, bloody sputum. Examination showed both lungs full of bubbling râles. It was difficult to hear the heart sounds because of the pulmonary edema. The blood pressure was 160 systolic and 96 diastolic and dropped to 130/90 following phlebotomy of 300 c.c. There was slight improvement following this procedure. The cardiac rhythm at this time was found to be totally irregular. Muscle tone was poor and there was no accentuation of the aortic second sound. It was difficult to evaluate the question of cardiac murmurs because of the pulmonary edema.

Autopsy Protocol. The heart weighed 500 grams. The mitral orifice admitted the tip of the index finger. On section the posterior and lateral wall of the left auricle was covered with a large, friable, grayish-brown, laminated thrombus which was firmly adherent to the auricular wall and when pulled away left an irregular granular surface. The mitral valve was grayish-white in color, opaque and rigid, and in several areas calcified. The chordae tendineae were markedly thickened, reduced in number, pearly-gray in color and shortened. The aortic semilunar valves were likewise grayish-white in color and rigid. There were adhesions between the cusps, with definite encroachment upon the lumen. The cusps adjacent to the right coronary orifice showed calcification. The septum membranaceum was grayish-white in color and semirigid. The section of the ventricle showed the musculature to be brick-red. Both right and left coronary arteries showed patent orifices with moderate diffuse atheromatosis distributed throughout their major branches. The aorta showed moderate diffuse atheromatosis which was slightly more marked at the lower end of the abdominal portion.

Comment. This patient had no known previous history of rheumatic fever and had no manifestations of disease until a few hours prior to admission to the hospital, when he suddenly developed acute symptoms of cardiac failure and went rapidly downhill despite all therapy. Atherosclerotic changes in the coronary arteries and aorta were rather mild. The extensive calcific changes were limited to the aortic and mitral valves and their respective rings. The extensive changes in the chordae tendineae and the papillary muscles are highly suggestive of previous rheumatic infection.

Case 7. W. L., a white male adult of 84 years, was admitted to the hospital on January 31, 1936, with a history of increasing dyspnea, ankle edema and nocturia of five months' duration. For five days prior to admission he complained of "very marked weakness." The essential findings on physical examination were the numerous râles throughout both lung fields, decrease in intensity of all heart sounds, absence of apical impulse, pulse rate of 40, moderate degree of ankle edema and a blood pressure of 140 systolic and 70 diastolic. Electrocardiographic study showed a complete heart block with auriculo-ventricular dissociation. The patient lapsed into coma soon after arrival at the hospital, developed Cheyne-Stokes respiration and died 50 hours after admission.

Autopsy Protocol. The heart weighed 575 grams. The left ventricular wall was hypertrophied and dilated, measuring 1.8 cm. in thickness. Multiple areas of fibrosis were present in both ventricular walls. The aortic valve was rigid and diffusely calcified. There was an old thrombus formation in the right coronary artery, 5 cm. from its origin. The left coronary artery and branches were patent. There were small areas of fibrosis in the interventricular septum.

Comment. The fibrosis in the interventricular septum was probably due to extension of calcific changes from the aortic valve and ring. This fibrosis in the interventricular septum, we believe, was responsible for the changes in the cardiac rhythm (auriculo-ventricular dissociation, with complete heart block).

Case 8. E. N., a white female adult, 74 years of age, was admitted to the hospital on March 1, 1932, with a history of "heart trouble for the past six months." There was progressive shortness of breath and increasing edema of the lower extremities. She had been taking tincture of digitalis before admission to the hospital. Three days prior to hospitalization she became semistuporous. On admission to the hospital she was found to be in stupor, markedly dyspneic and cyanotic. The heart was enlarged to the left. The apex was in the sixth interspace, outside the nipple line. The sounds were totally irregular with a marked rough systolic murmur heard over the entire precordium. There were râles at both bases. The liver was enlarged to two fingers-breadth below the costal border and the edema of both lower extremities extended upward almost to the groin. Patient died within 12 hours after admission to the hospital, without rousing from coma.

Autopsy Protocol. There was marked thickening of the left ventricle which bulged into the lumen of the right ventricle. The mitral orifice admitted only one finger. The aortic semilunar valve was markedly sclerotic and in the anterior cusp there was a calcified nodule about 1 cm. by 0.5 cm. Both coronary arteries were patent. The descending thoracic aorta showed calcified plaques about one-half inch to one inch in length.

Comment. This patient had suggestive evidence, on postmortem examination, of a healed rheumatic mitral valvular disease (stenosis). There was a six months' history indicative of congestive heart failure. The calcification present was confined to the aortic valve leaflet.

Case 9. J. S., a white male adult, aged 65 years, was first admitted to the hospital in 1934, for gastric distress following meals. At this time a loud systolic musical murmur was heard over the entire precordium, especially intense over the aortic area and transmitted to the vessels of the neck. The second sound at the aortic area was diminished in intensity. Roentgen-ray study revealed cardiac enlargement and sclerosis of the aorta. His stay at the hospital was uneventful and he left against

advice. Two years later, in 1936, he was readmitted because of increasing dyspnea, orthopnea and nosebleeds. The blood pressure at this time was 170 systolic and 105 diastolic, and the cardiac findings were essentially the same as those noted previously. There were numerous râles at both bases, and the pulse rate on admission was increased (rate 120). Electrocardiographic study showed a marked degree of left axis deviation with evidence of myocardial damage. Digitalis therapy and rest in bed brought about a striking improvement and the patient left the hospital five days after admission, much improved. He was readmitted to the hospital for the third time on January 5, 1937, some six months following previous discharge. Marked dyspnea and orthopnea, aggravated by a recent upper respiratory infection, brought him to the hospital. At this time there was evidence of congestive heart failure as manifested by numerous râles in both bases, fluid in the right chest, enlargement of the liver, fluid in the peritoneal cavity and edema of the ankles. The heart was definitely increased in size and a rough systolic murmur, most intense over the aortic region, was heard over the entire precordium, and was transmitted upward into the vessels of the neck. There was a systolic thrill over the aortic area. The second aortic sound was absent. Digitalis therapy and sedation failed to bring about any improvement and there was gradual increase in the signs of heart failure. The patient died two weeks after admission.

Autopsy Protocol. The heart weighed 600 grams. The visceral pericardium was adherent to the parietal pericardium at one point on the anterior surface of the left ventricle. Over the entire apex and over the septum there were irregular grayish-white areas immediately beneath the mural endocardium. At a point one-third down on the septum the left ventricle showed a sudden transition from the normal mural endocardium to a raised, firm, grayish-white lining. The wall of the ventricle thinned out as the apex was approached (thickness of 4 mm.). The entire apex was ballooned and filled with an irregular laminated thrombus. The aortic semilunar valves were rigid, opaque, and showed numerous raised areas bright yellow in color, some of which were bony hard in consistency. The area between the left anterior cusp and the anterior mitral flap showed a similar calcification. The base of the aorta showed diffuse atheromatosis with calcification. The coronary orifices were both patent. The anterior branch of the left descending coronary artery was completely occluded from a point 3 cm. from its origin and for a distance of 1.5 cm. This length of the artery contained a thick, completely occluding calcific node. Distal to that point, the vessel was of average appearance. The circumflex branch of the left coronary artery showed a moderate sclerosis. The right coronary artery was likewise completely occluded at a point 6 cm. from its origin and for a distance of 1 cm.

Comment. This patient had hypertensive heart disease with extensive sclerotic changes in the coronary arteries with evidences of old and recent occlusion. The extensive calcification of the aortic valves undoubtedly contributed in some degree to the increasing cardiac insufficiency. The clinical course in this case was primarily influenced by the changes in the coronary system.

Etiological Factors

The causes of calcareous aortic stenosis are commonly ascribed to:

1. Degenerative changes incident to atherosclerosis.
2. Rheumatic fever.
3. Healed infective endocarditis.
4. Changes superimposed upon a congenital defect of the aortic valves.

1. Atherosclerosis. In 1672 Rayger [12] first described calcification of the aortic valves. A detailed pathological description was first given by Moenckeberg [5] in 1904. He described in detail the pathogenesis and morphology of aortic stenosis with calcareous deposition. This author called attention to the fact that lesions of an atherosclerotic nature affecting the valves regularly begin to appear beyond the age of 35 years. In the atherosclerotic group, Moenckeberg [5] described an "ascending valve sclerosis" wherein the changes take place in the layers of the valve facing the sinus of Valsalva, from which point the process extends up the valve leaflet to the free margin. He also described a "descending type" where the lesion starts primarily in the aorta and extends down onto the valve leaflet and commissures. The fact that calcareous aortic stenosis is seen most frequently beyond the age of 50 would indicate that the most common cause of these changes is atherosclerosis. However, even when there are most advanced calcific deposits in the aortic valves with concomitant lesions in the aorta or coronary arteries or both a non-infective basis of the disease cannot be assumed. The difficulty in evaluating the question of atherosclerosis or infection as factors has been well stressed by Hathaway [8] in his summary of 52 cases.

2. Rheumatic Fever. The fact that calcareous aortic stenosis is seen in the age group in which active endocarditis seldom occurs would make it appear that degenerative heart disease and the atherosclerotic changes associated with the degenerative processes are the most frequent causes of calcific changes in the aortic valves. The difficulty in obtaining any definite history of rheumatic infection in many cases also favors this concept. It is proper to call attention to the fact that, since this group is farthest removed from that period of life during which active rheumatic fever is common, evidences of active rheumatic disease are not to be expected either on clinical examination or at postmortem examination. The failure to elicit a history of previous rheumatic disease is not unusual, for even in mitral stenosis, which is almost always due to rheumatic fever, a history of such infection is obtained only in about 50 per cent of the cases according to the analysis of Christian.[6] In an excellent survey of 123 cases of aortic stenosis McGinn and White [11] report a previous history of rheumatic fever in one-third of the entire group. There was a definite history of rheumatic infection in 23 per cent of those who came to autopsy and in 46 per cent of the clinical series. Cabot [4] concluded that his cases were due to previous rheumatic disease but could not very well correlate the age and sex incidence with rheumatic fever. In none of our cases was there any history suggestive of previous rheumatic infection. In Cases 2 and 8 of our series the probability of previous rheumatic disease must be considered even though there were concomitant evidences of degenerative changes.

3. Healed Infective Endocarditis. We are indebted to Libman [9, 23] for our knowledge concerning the relationship of healed subacute bacterial endo-

carditis to chronic valvular defects. According to Libman's [23] concept healing of the valve takes place after the patients become bacteria-free. Subsequently, calcific masses are deposited in the valves which interfere with their function. In these cases there is usually a history of a primary valve infection complicating the rheumatic phase. This is followed by a free interval of months or years with subsequent reinfection of the diseased valve, commonly by the *Streptococcus viridans*. The clinical course at this stage may be that of a severe active bacteremia, or the infection may be very low grade and run a protracted clinical course. If healing takes place there may be evidence only of a valvular defect. Case 4 of our series presented the following pathological feature which leads us to believe that it belongs in this group of healed infective endocarditis. This patient had an aneurysm of the hepatic artery and areas of infarction in the kidney and in the spleen, in addition to the calcification of the aortic and mitral valves. The opinion that bacterial endocarditis may be healed by calcification was recently expressed by Perry.[13] This author states that it is probable that in those cases where calcific nodes are found on one of the cusps of the aortic valve, in the absence of atheromatosis, an unrecognized active bacterial endocarditis later healed may have been the cause. The presence of old renal infarcts, the absence of pericardial adhesions, and the fact that both diseases (calcareous aortic stenosis and subacute bacterial endocarditis) predominate in males, are, in the opinion of Cabot,[4] suggestive evidence of healed subacute bacterial endocarditis.

4. Congenital Defects. We are greatly indebted to Osler [14] for the present day knowledge of the relationship between a congenital defect (bicuspid aortic valve) and the development of calcareous aortic stenosis. The predisposition of this type of congenital lesion to calcific deposition or the occurrence of superimposed infection was shown by Osler and by Abbott.[15] In Case 5 of our series we have all the criteria as laid down by Osler for the identification of congenital bicuspid valve. We believe that the deposition of calcium in this case was engrafted upon a congenitally defective valve in which infection did not occur. Careful search of other organs and viscera failed to reveal any presumptive evidence of a previous endocarditis. Recent analysis of nine cases [16] of congenital bicuspid aortic valve indicate the marked tendency for calcific deposition in these individuals. In our patient there were no other congenital abnormalities either in the cardiovascular system or elsewhere, other than in the bicuspid aortic valve. Syphilitic changes in the aorta with the subsequent pathological changes involving the aortic valves never result in a stenotic lesion of this valve.

Clinical Features

The murmur of calcareous aortic stenosis may be described as extremely loud and may be either musical or hard and saw-rasping. At times this murmur may be so loud that it may be heard; to quote Stokes,[17] " at some

distance and with a patient resting in a chair, the thrill may be transmitted to the arms of the chair." The radiation of the murmur is classical. Invariably the direction is upward and to the right side of the neck, and at times the murmur may be heard in the paravertebral area on the right side posteriorly at the level of the second thoracic vertebra. If there is associated calcification of the mitral ring there may be a loud systolic murmur heard at the apex.[22] This murmur radiates upward along the left sternal border and, as described by Libman,[22] becomes intensified over the aortic area. The apical murmur under these circumstances is also transmitted to the left axilla.

A distinct thrill over the aortic area is usually present in calcareous aortic stenosis. The thrill at times is more perceptible when the patient is in the upright position. The character of the second aortic sound is an important consideration in the diagnosis. The absence of the second sound or a marked diminution in its intensity is the most important single confirmatory sign in calcareous aortic stenosis. This is especially true if hypertension exists. At times the second sound is replaced by a soft blowing diastolic murmur. In our studies we have not encountered any signs of clinical insufficiency of the aortic valve.

The advanced age of the average patient is such that changes in the wall of the radial artery make the detection of fine differences in pulse excursion rather difficult. We, therefore, did not place much importance on the presence of the typical pulse of aortic stenosis (rarus, parvus, tardus and longus). Information gained from the study of the blood pressure values was not significant for the reason that this factor is dependent on too many variables (insufficiency of the left ventricle, myocardial tone, condition of the peripheral vessels, etc.).

Angina as a prominent symptom in calcareous aortic stenosis has recently been reported by Boas.[18] This author stressed not only the symptom of precordial pain but also called attention to heart-block and a tendency to syncope in this group. In view of the high incidence of associated calcification of the coronary arteries with some resultant insufficiency, it is not surprising that angina pectoris is a frequent clinical feature. Pain has been known to be accompanied by sudden death, with or without changes in the rhythm. When the changes in the annulus fibrosus extend into the membranous portion of the septum, changes in cardiac rhythm are to be expected. Partial or complete block or bundle branch block may follow if this septal process takes place in the angle between the anterior cusp and the right posterior cusp, at which site the conduction tissue is located.[19] In a patient who had calcareous aortic stenosis with attacks of syncope, Marvin and Sullivan [20] obtained electrocardiographic tracings during the period of syncope. They concluded that these attacks of syncope were due to an abnormal carotid sinus reflex. This is of practical clinical importance especially in undertaking an operation upon an elderly patient who shows signs of calcareous

aortic stenosis. Sudden death while under anesthesia may be due in these patients to an abnormal carotid sinus reflex or rhythm changes. Sudden death in Case 3 (N. W.) could not be explained by any morphological changes. A mechanism such as that described by the above authors might be invoked in this death. The sudden deaths which occurred in Cases 2 and 9 were due either to acute coronary artery occlusion or to extension of the calcification from the aorta to the coronary arteries.

Summary

Calcareous aortic stenosis is a disease predominantly affecting males and usually occurring past middle life, but occasionally encountered in younger persons. The outstanding physical signs are the typical murmur, accompanied by a diminished second aortic sound and a palpable thrill over the aortic area. The heart is enlarged. The stenotic aortic lesion is usually accompanied by changes (atheromatous) in the aorta and coronary arteries and at times by calcific changes in the mitral valve and ring. The syndrome of angina pectoris and disturbances in cardiac rhythm are commonly seen in this disease. The occurrence of sudden death is a striking and frequent characteristic.

In this communication we have reported nine cases of calcareous aortic stenosis and have discussed the etiological factors, morphological changes and clinical features.

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THE DETERMINATION OF BILIARY TRACT INFECTION WITH THE ENCAPSULATED DUODENAL TUBE *

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THAT it is now possible to determine biliary tract infection with considerable accuracy, without operation, has been proved by the correlated pre-operative and operative bacteriological findings in a series of 120 patients with chronic biliary tract disease. In each case a pre-operative duodenal drainage was performed under sterile precautions with the encapsulated Twiss duodenal tube,[1] and the bacteriological findings of the duodenal bile were compared with those of specimens obtained from the biliary tract at operation. The findings were identical in such a large proportion of the cases studied that the use of this procedure as a diagnostic measure seems fully justified.

The importance of being able to ascertain infection of the biliary tract cannot be overestimated. The excellent results of early surgery in patients with infection are well known, likewise in those with stone, obstruction, or malignancy. On the other hand, careful follow-up studies have shown that in the absence of these conditions, surgical treatment frequently gives unsatisfactory results. We believe that this can be attributed in many cases to an inability to determine the presence pre-operatively of biliary tract infection. Another reason is disregard for functional disorders or dyskinesias of the biliary tract, usually not associated with infection, which were first described by Westphal[2] and by Ivy and Sandbloom.[3]

In biliary tract disease reliable evidence of infection can be obtained only by isolation of pathogenic bacteria upon culture. This is possible by the use of the duodenal tube, which was introduced by Gross[4] and Einhorn,[5] and greatly improved in diagnostic value by the Lyon[6] method of duodenal intubation. Further contributions have been made by Rehfuss,[7] Levine,[8] and many others. The reliability of diagnostic duodenal drainage is dependent upon a recognition of the fact that the normal fasting duodenum is sterile, as established by the investigations of Cushing and Livengood,[9] MacNeal and Chace,[10] and Kellogg.[11] The value of cultures taken under proper precautions in establishing a diagnosis of biliary tract infection has been recognized for many years; among early contributors to the literature should be mentioned Lyon,[6] MacNeal and Chace,[10] Smithies,[12] Whipple,[13] and Garbat.[14]

Infection as a cause of disease of the gall-bladder and bile ducts has long been recognized. Early experience in surgical treatment showed a very high

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incidence of infection. More recent reports, however, have shown a distinctly lower percentage of positive cultures in the gall-bladder removed at operation. This is probably partly due to improved methods of diagnosis, which have led to the earlier recognition and surgical treatment of those patients having definite cholecystitis. Early treatment has probably many times prevented the element of infection from being superimposed upon other conditions, such as functional disturbances or cholelithiasis.

The actual incidence of biliary tract infection, as demonstrated from bacteriological cultures made at the time of operation, can be shown by a study of the literature. In regard to the bacteriological findings in bile removed from the gall-bladder at operation, Hartman [15] in 1903 reported an incidence of infection of 78 per cent, Rosenow [16] in 1916 55 per cent, Rovsing [17] in 1923 11 per cent, Judd, Mentzer, and Parkhill [18] in 1928 31 per cent, Branch [20] in 1929 reported 19 per cent. Hanssen and Yurevich [21] found in a series of 104 cases studied in 1935 that 20 per cent of operative bile specimens showed positive cultures. In the authors' present series of 120 patients the incidence of infection in the biliary tract as a whole was 24 per cent.

A complication in the pre-operative determination of biliary tract infection is the known fact that positive cultures may be obtained in a higher percentage of cases from the gall-bladder wall than from the gall-bladder bile. Thus Judd, Mentzer, and Parkhill [18] found positive bile cultures of the gall-bladder bile in 15 per cent of a series of 200 cases, whereas the gall-bladder wall proved positive in 40 per cent. Other investigators, however, have found lesser degrees of difference. Moynihan [19] reported 31 per cent positive cultures in the gall-bladder bile, 37 per cent in the gall-bladder wall. Branch [20] found the respective incidence of infection to be 19 per cent and 25 per cent, Hanssen and Yurevich [21] obtained 20 per cent positive cultures from the gall-bladder bile, 30 per cent in the gall-bladder wall.

In the past duodenal drainage has not proved entirely accurate as a means of demonstrating biliary tract infection. In 1921 Whipple [13] reported, in a series of 26 cases, a 50 per cent correlation between the cultures obtained at operation upon the biliary tract and those obtained in duodenal drainage cultures pre-operatively. In 1934, Lyon [6] reported that in 101 cases coming to operation the organisms found at operation had been found present in duodenal bile in the majority of cases; a detailed study of bacterial cultures was not reported.

The most detailed of the pre-operative and operative bacteriological studies which has come to our attention is that of Hanssen and Yurevich [21] of this clinic, who reported a series of 104 operative patients in 1935. In this group duodenal drainage cultures were sterile in 25 per cent of the cases, whereas at operation the biliary tract proved to be entirely sterile in 67 per cent of the patients. Therefore duodenal drainage indicated infection in 75 per cent of the patients, whereas operation proved infection in only 33 per cent. Furthermore 75 per cent of the positive duodenal cultures showed a

mixed growth of three or more types of organisms, while at operation only 5 per cent of the cases showed more than one. The predominating bacteria at operation were *B. coli*, streptococci, *B. typhosus*, and staphylococci. The duodenal cultures were predominantly staphylococci and streptococci.

The duodenal drainage reports of Hanssen and Yurevich [21] with 25 per cent sterile cultures, compare very favorably with other reports of similar work. The highest incidence of sterile cultures of duodenal bile in the literature is that of Buttiaux,[22] who in 1931 reported a series of 50 cases, with 42 per cent negative cultures. Garbat [14] in 132 cases found sterile cultures in 38 per cent, Whipple's [13] series has 15 per cent sterile cultures preoperatively. In 1935 Lyon [6] reported a series of 905 drainages, having an incidence of 15 per cent sterile cultures. An extensive discussion has been published by Rehfuss and Nelson.[23]

These findings led Hanssen and Yurevich [21] to the conclusion that "the present technic for the bacteriological study of bile obtained by duodenal drainage is unsatisfactory because of the frequent occurrences in cultures of contaminating organisms from the pharynx, buccal cavity, and stomach." They further stated that "a technic must be developed which will eliminate or reduce to a minimum the confusion due to the presence of such contaminating organisms before cultures of bile obtained by duodenal drainage can be depended upon to supply reliable evidence of infection of the biliary tract."

Shortly after this publication Twiss and Phillips [24] reported an improved method of obtaining specimens of duodenal bile by means of an encapsulated duodenal tube.[1] The preparation of the tube and its use have been described in detail by Carter, Greene and Twiss.[25] In short, the bucket of a sterilized Twiss duodenal tube is covered with a keratin-coated gelatin capsule, which is dissolved off after the tube has entered the duodenum. Contaminations at the syringe end of the tube are eliminated as far as possible by the use of a 3-way stop-cock, through the side arm of which the bile for culture is collected.

The superiority of the encapsulated method in obtaining bile specimens for culture was demonstrated in the introductory article. A comparative study was then reported of 165 drainages upon a series of 50 patients, using both the encapsulated and "open" methods. The encapsulated method gave a considerably higher incidence of sterile cultures and more cultures of organisms significant of biliary tract infection than that found with the "open" method. Furthermore the encapsulated method gave a lower proportion of mixed cultures and types of organisms found in throats and gastric contents of the same patients.

Since this article was published there have been few reports in the literature about investigations of this character. Among these should be mentioned that of the German clinicians Kopnic and Melnik,[26] concerning the generally conceded diagnostic value of duodenal drainage in typhoid fever, and the favorable results of the Italian Repetto [27] in the diagnosis of active infections of the extra-hepatic biliary tract.

Pursuant upon the report of Twiss and Phillips [24] it is now our purpose to evaluate the results which have been obtained in a series of 120 consecutive operative cases which were studied in the Biliary Tract Clinic of the New York Post Graduate Hospital. In each case one or more pre-operative duodenal drainages were performed by the encapsulated method; the duodenal or dilute and the concentrated specimens of bile obtained were cultured under

TABLE I

Bacteriological findings in cultures of duodenal bile, 120 consecutive cases.

	Number of Cases	Per Cent
All cultures sterile	75	63
Positive cultures, 1 or 2 types of pathogenic organisms	32	26
Positive cultures, 1 or 2 types of non-pathogenic organisms	2	2
Positive cultures, 3 or more types of organisms	11	9
Total	120	

TABLE II

A comparative study of cultures of duodenal bile and specimens obtained from the biliary tract at operation.

Bacteriological Findings			
Number of Cases	Duodenal	Operative	%
Sterile Cultures of Duodenal Bile			
74	Negative	Negative	62
1	Negative	Positive	1
Total 75			
Positive Cultures of Duodenal Bile			
20	Positive	Positive identical	17
5	Positive	Positive similar	4
3	Positive	Positive different	2
17	Positive	Negative	14
Total 45			

the supervision of Dr. Adele Sheplar of the Department of Bacteriology. At the time of operation, specimens for culture were obtained of the gall-bladder bile, the gall-bladder wall, the cystic duct node, and stones if present. In patients having a choledochotomy, bile was taken from the common duct for culture. Evidence of infection was considered to be the presence of positive cultures of bacteria in any part of the biliary tract, or in any specimen of duodenal bile.

The results of the duodenal drainage cultures are shown in table 1. It is here seen that sterile cultures were obtained in all specimens of duodenal bile in 75 patients or 63 per cent of the series, and one or two types of organisms considered significant of biliary tract infection in 32 patients or 26 per cent. It is therefore apparent that findings considered satisfactory for diagnostic purposes were obtained in 89 per cent of the patients, whereas contaminations (non-pathogenic or mixed growths of bacteria) resulted in but 11 per cent.

A comparative study of bacteriological cultures of duodenal bile and of the specimens obtained at operation is shown in table 2. Here it is seen that 74 of the 75 patients having sterile cultures of duodenal drainage bile proved to have sterile cultures from all parts of the biliary tract at operation.

TABLE III

An analysis of the 28 patients having positive cultures in both the duodenal bile and operative specimens, showing the types of organisms found in the duodenal bile and in the biliary tract at operation.

	Bacteriological Findings	
Number of Cases	Duodenal Drainage	Operative
8	Colon bacillus	Same
2	Colon bacillus-streptococcus	Same
8	Typhoid bacillus	Same
1	Non-hemolytic streptococcus	Same
1	Staphylococcus-streptococcus	Same
1	Colon bacillus-staphylococcus	Colon bacillus-streptococcus
1	Colon bacillus-streptococcus	Colon bacillus
1	Streptococcus-staphylococcus	Streptococcus
1	Colon bacillus-staphylococcus	Colon bacillus
1	*Bacillus proteus*-streptococcus	*Bacillus proteus*-streptococcus staphylococcus
1	Colon bacillus	Non-hemolytic streptococcus
1	Colon bacillus	*Bacillus proteus*
1	Streptococcus	Staphylococcus
Total 28		

Of the 28 patients having positive cultures both in the duodenal bile and in the biliary tract, 25 had the same type of organisms in the biliary tract that had been cultured in the duodenal bile. Of the remaining 20 patients having positive cultures of the duodenal bile, 17 were negative at operation and 3 showed organisms in the biliary tract different from those in the duodenal drainage bile.

An analysis of the 28 cases in which positive cultures were obtained in both the duodenal bile and the operative specimens is given in table 3. In 20 cases identical types of organisms were found in both the duodenal bile and the operative specimens, even when two types of organisms were found in the biliary tract at operation. In five patients two types of organisms were

found in the duodenal bile, whereas the operative specimens showed but one of these. In only three cases of this group, or 2 per cent of the entire series was there no agreement between the duodenal drainage and operative findings.

A summary of the 18 cases in which either positive or negative bacteriological findings in the duodenal bile were not confirmed at operation is given in table 4. In only one patient (number 46) a single sterile pre-operative specimen was not confirmed at operation. The biliary tract here showed a streptococcus. Seventeen other patients had positive cultures of duo-

TABLE IV

A summary of 18 cases in which the pre-operative and duodenal drainage cultures were at variance with the operative cultures. "M" specimens are obtained following stimulation with magnesium sulphate, "O" specimens after olive oil. ("Mixed" cultures are those having three or more types of bacteria.)

	Bacteriological Findings	
Case Number	Duodenal Drainage	Operative
29	Mixed—all three specimens	Negative
30	Mixed—all three specimens	Negative
31	Non-hemolytic streptococcus in the M-1 specimen only O-1 and O-2 negative	Negative
32	Mixed D-1 and M-1 specimens O-1 and O-2 negative	Negative
33	Mixed D-1 specimen only O-1 specimen negative	Negative
34	*Micro. catarrhalis*-streptococcus in D-1 only	Negative
35	Friedlander bacillus	Negative
36	Colon bacillus	Negative
37	Mixed—in all specimens	Negative
38	Mixed—in all specimens	Negative
39	Mixed—in all specimens	Negative
40	Mixed—in all specimens	Negative
41	Mixed—in all specimens	Negative
42	Colon bacillus in all specimens	Negative
43	Mixed—one specimen only	Negative
44	Streptococcus in D-1 only O-1 and M-1 negative	Negative
45	Mixed in all specimens	Negative
46	Negative—only D-1 cultured	Streptococcus

denal bile; in each the biliary tract was sterile at operation. The cultures labelled "mixed" were considered contaminations at the time of the drainage because of the presence of three or more types of bacteria, a finding never confirmed at operation. This conclusion seemed further justified because in most of these patients there were organisms in the duodenal bile such as the *Micrococcus catarrhalis,* pneumococcus, Friedlander bacillus, or the *Staphylococcus albus,* which are rarely if ever found in the biliary tract at operation.

Taking into consideration all cases in which the duodenal drainage bacteriological findings were not confirmed at operation, there was disagreement between the duodenal drainage and operative findings in 21 cases or 17 per

cent, of the total series. The diagnostic accuracy of the duodenal drainage findings may therefore be considered to be 83 per cent. By eliminating the 13 cases of disagreement obviously due to contaminations of duodenal bile, the diagnostic accuracy of those drainages considered satisfactory is increased to 93 per cent. It is hoped that more experience with the encapsulated method will further reduce the incidence of contamination of the duodenal bile.

Summary

1. In a series of 120 operative patients with chronic disease of the gall-bladder diagnostic duodenal drainages were performed pre-operatively, using the encapsulated Twiss duodenal tube.

2. Bacteriological cultures were made of the specimens of dilute and concentrated duodenal bile and of specimens obtained at operation from the gall-bladder bile, the gall-bladder wall, the cystic duct node, and stones if present.

3. Positive cultures were considered to be evidence of infection when found in any specimen of duodenal bile or in any part of the biliary tract.

4. A comparison of the pre-operative and operative bacteriological findings gave the following results:

(*a*) Sterile cultures of duodenal bile were obtained in 75 cases, in 74 the biliary tract proved sterile at operation.

(*b*) Positive cultures of duodenal bile without evidence of contamination were obtained in 28 cases, in 25 the same types of organisms were found at operation.

(*c*) Positive cultures of duodenal bile were obtained in 17 patients having a sterile biliary tract at operation, in 13 there was evidence of contamination of the duodenal bile.

5. The pre-operative diagnostic bacteriological findings were confirmed at operation in 83 per cent of the cases. Disregarding drainages considered unsatisfactory because of contaminations, the pre-operative and operative findings agreed in 93 per cent. Bacteriological cultures of duodenal bile obtained under sterile precautions, by means of the encapsulated duodenal tube, afford reliable evidence of biliary tract infection.

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HORMONAL THERAPY FOR THE TREATMENT OF HIRSUTIES

A Preliminary Report *

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ALTHOUGH it is true that to date physiotherapy has been the chief means employed in the treatment of hirsuties and hypertrichosis in females, it is obvious that, whereas it has its merits, it is a form of therapy which does not in any way take cognizance of the etiological factors involved. Although it is true that the etiological factors in hirsutism and virilism have not been definitely established, there is sufficient evidence as found by many investigators to indicate that the root of this disturbance is a glandular dyscrasia which usually can be associated with a disturbance of the adrenals, the ovaries or the pituitary. The recession of masculine characteristics, even though temporary, which ensues after removal of an adenoma of the adrenal or of the ovary, or the recession or abatement of masculinizing characteristics which ensues after resection, in whole or in part, of a hyperplastic adrenal gland, suggested to investigators that it is a glandular derangement probably caused by the neoplasm or by the hyperplasia.[1]

I, too, believe that there is a glandular derangement involved in cases presenting hirsutism and masculinization even where no neoplasm is apparent. In a series of eight cases of hirsutism which I studied, I found that treatment with hormonal therapy in an attempt to regain glandular balance produced some surprising and promising results.

As a result, I am presenting for consideration the histories of this group of eight cases of females who presented such hirsuties and other masculinizing characteristics. My choice of cases for this series was in no way influenced by the results obtained with hormonal therapy; these cases were included merely because of the consecutive order in which they appeared for treatment when this study was undertaken.

The therapy administered by me in this series of aneoplastic glandular cases presenting hirsuties was based upon some of my own clinical observations, as well as upon the findings of Zondek, and Greenwood and Blythe; it was also in line with the observations and suggestions of Kurzrok. Zondek,[2] in his observations, found that estrone is rapidly absorbed when administered cutaneously. Greenwood and Blythe [3] found that the type of feathers in the capon could be modified by the cutaneous injection of estrone, so that at the local site of such injection the feathers changed to those of the hen, whereas the rest of the feathers on the body surface remained those of a capon. Kurzrok [4] and his associates found that the skin was very susceptible to the action of male hormone, so that in consequence it might re-

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spond by hirsutism even in the absence of any other masculinizing features. In hirsute females showing verified adrenal neoplasm and adrenal hyperplasia, Kurzrok[4] and other investigators[5] found that there is a preponderance of male hormone being produced in such cases, presumably by the hyperfunctioning adrenals, which checks the normal amount of female sex hormone that is being produced by the ovary. Kurzrok therefore suggested the possibility of suppressing the male hormone production by injections of estrone or its derivatives, not only by intracutaneous injection, but by inunction directly to the skin.

In view of the above, I attempted in my series the use of estrone by inunction and by hypodermic administration in some cases in an attempt to modify the hirsute areas directly and to flood the system with a product of the ovary in order to counteract the effects of the hyperfunctioning adrenal. In addition, in others, I attempted the use of a gonadotropic factor of the anterior pituitary gland, in an attempt to provoke stimulation of the ovary directly. By using the various types of therapy, I hoped to be able to study the responses to the varied therapy, both estrogenic and gonadotropic, and thus evaluate, if possible, the effects and benefits, if any, of these products in females presenting hirsuties and other masculine characteristics.*

Case 1, aged 15 years, was referred for treatment because of hirsuties. She presented an overgrowth of moderately long, black, coarse hairs on the upper lip, chin, thighs and legs. Her menstruation had started one year ago, at the age of 14 years; it was regular for a while, but now occurs only every two to three months.

The patient was of the tomboy type. Her walk, dress, and mannerisms tended toward the masculine type. She did not like boys, but liked to partake of boys' games and was quite athletic.

The patient was obese, weighing 168 pounds; her height was 64 inches. The upper measurement (as measured from the top of the pubis to the heel) was 30 inches, the lower measurement (as measured from the top of the pubis to the vertex of the head) was 34 inches—a eunuchoid proportion. Her voice was gruff.

The mammae were prominent and contained glandular tissue. The labia minora were hypertrophied; the clitoris was enlarged to about 2½ cm. after retraction of the surrounding foreskin. The suprapubic hair was heterologous in distribution extending up to the umbilicus. Axillary hair was present. There was apparently no gross evidence of neoplasm in the pituitary, adrenals, or ovaries.

Roentgen examination revealed a closure of all epiphyses of the hand, wrist and elbow, and an apparently normal skull and sella turcica. The only significant chemical finding in the fasting blood was a cholesterol of 195 mg. and glucose of 86 mg. The Wassermann reaction was negative. The basal metabolic rate was plus 3 per cent at the outset of treatment. (At the end of treatment, it was minus 13.6 per cent and minus 9 per cent.)

An estrogenic hormone in small doses was given by hypodermic three times a week. After about two months of treatment there were slight but definite areas on the inner and anterior aspects of the thighs that were free from hair.

* The amniotin for hypodermic use and in ointment form was supplied by E. R. Squibb & Sons, the theelin by Parke, Davis & Co., the progynon B by Schering Corporation—all estrogenic hormones. The emmenin—a placental extract of Collip having primarily estrogenic properties and some gonadotropic-like effect, for oral use, and an anterior pituitary gonadotropic factor (which contains also small amounts of other hypophyseal factors), were supplied by Ayerst, McKenna & Harrison.

An estrogenic ointment (this ointment contained 1000 I.U. per gram of substance) was then applied daily for about one month to the hairy region of the face, and to parts of the thigh, in addition to the hypodermics of estrone. The only appreciable effect resulting from the use of the ointment was a breaking off of some of the hairs at these local sites, but the roots remained. On the whole, the skin of the face became somewhat clearer, but there was no other effect except that the hair on the face seemed somewhat bleached. With this combination therapy the extension of the suprapubic hair to the umbilicus was still present, but the hair on the legs, though still present, showed areas of sparseness. After one month ointment was discontinued, but the hypodermics were continued for another two months.

At the termination of five months of treatment the patient had lost about 20 pounds on a restricted diet. Her menstrual periods were still irregular during the treatment. The clitoris was still prominent; the voice was not as gruff as originally; her gait and carriage seemed more feminine. The mother said that the patient was beginning to show an attraction for the opposite sex.

A report from her friends about one month after discontinuation of treatment indicated that she seeks the company of males, mixes well with females, uses rouge and face powder and even thinks of knitting. (These were foreign to her before.)

One and a half years later, at the age of about 17, the patient was rechecked by me. She informed me that she goes out with the opposite sex, mixes well with those of her own sex. Her periods have been regular since the discontinuation of her treatment; her flow is good, lasting three to four days. However, there had been regrowth of hair since treatment had been discontinued. The hirsuties of her legs, thighs and face was still present.

Case 2, 23 and married, appeared for treatment of obesity and superfluous hair growth. She had been treated at times for various glandular conditions. The patient was nervous, irritable, tired easily and was "lazy." Her menstrual periods started at 12 years and had been regular since. Her libido was not disturbed.

She weighed 162 pounds, was 51 inches in height, and presented normal body proportions. There was a marked hair growth on both cheeks, upper lip, chin and neck, which the patient had been accustomed to bleaching, in addition to frequent shaving of the neck and chin. The thighs and legs were completely covered with hair; the suprapubic hair extended up to the umbilicus. The clitoris was not enlarged.

There was no evidence on examination of any neoplastic pathology. The sella turcica was normal. The basal metabolic rate was 0 and plus 27 per cent on two different occasions. A fasting blood sugar was 90 mg.

The patient was placed on a restricted diet, estrogenic hormone by hypodermic several times a week, a placental preparation—emmenin—by mouth, and estrogenic ointment to be used by inunction on the face (100 grams containing 100,000 I.U. were used).

After two months of this therapy the patient showed complete loss of hair on the cheeks and neck. There was an occasional loose hair still present on the chin, but shaving was no longer necessary. There were moderately large hairless areas on the back of each thigh. As a whole the patient was much better in spirit, was more energetic, and had lost some of her excess weight. Her menstrual periods were not changed by the treatment. A follow-up was not possible.

Case 3 (figures 1 and 2), aged 17, presented a marked hair growth on the cheeks and upper lip, and a moderate growth on her forearms, arms and legs. The patient dated the onset of the superfluous hair on her face from the age of 15, with more marked growth since that time. Her menstruation had started at 13 years of age, but was always irregular, skipping periods for several months. The periods were accompanied by headaches.

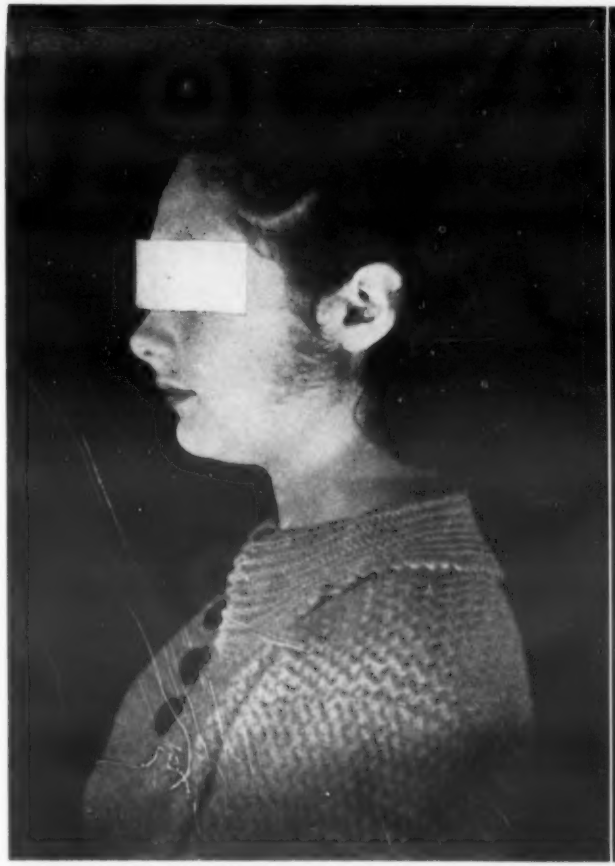

FIG. 1. *Case 3.* Before institution of therapy. Note hirsuties of cheek; much of the hirsuties is not apparent in the photograph.

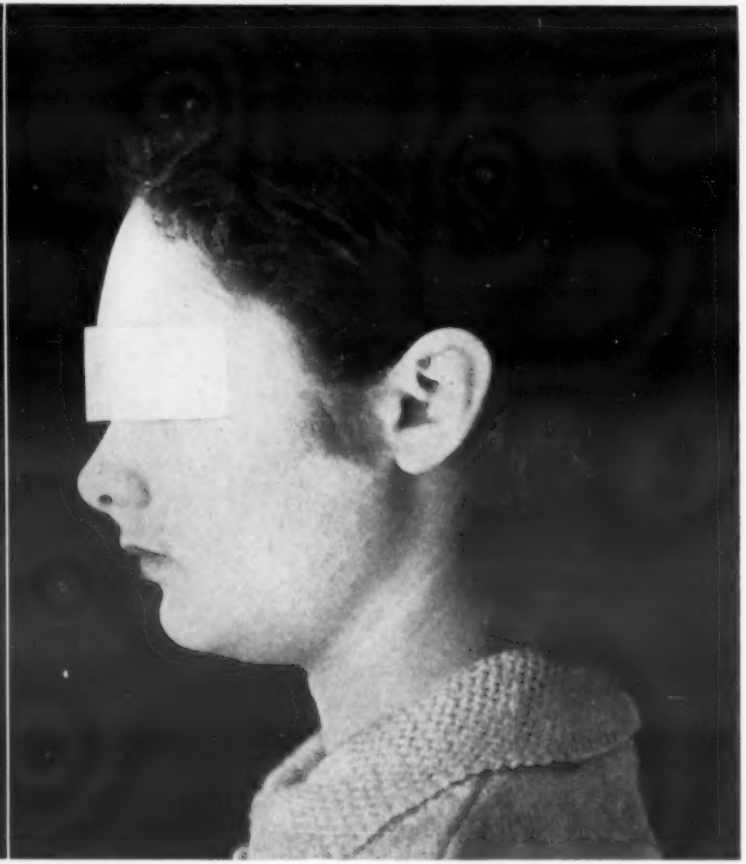

FIG. 2. *Case 3.* Five months after institution of hormonal therapy. Note complete loss of superfluous hair of face; note acne.

Her weight was 113½ pounds, but she was prone to gain weight very easily if she did not watch her diet; her height was 60½ inches. The lower measurement was greater than the upper. Axillary hair was present. There was a moderate amount of hair on the inner and posterior aspects of the thighs and legs which the patient removed by depilatories. There was some hair in the sacral region. Pubic hair was present with a slight extension to the umbilicus. The clitoris was not enlarged. The breasts were well developed.

Roentgenograms revealed no existing pathology of the skull; all epiphyses of the wrist, hand and elbow were closed. The basal metabolic rate was 0.5 per cent. Her fasting blood sugar was 77 mg.

The patient was given an estrogenic ointment by inunction of the face. She used 200 grams of the ointment (200,000 I.U.) in a period of four months. Here, too, as in the previous case, there was a breaking off of some of the hairs and a bleaching of the originally dark hairs. One month after the use of the ointment there appeared to be an acne of the right cheek, and therefore ointment was applied to the left cheek only.

After three months of treatment with the ointment, an estrogenic hormone in moderate doses was given by hypodermic in addition to the estrogenic ointment. After one month of the latter combined treatment, without any marked perceptible effect, the hypodermics were discontinued. Subsequently, the patient noticed that the hair on the right cheek, where application of ointment had been discontinued, had now become sparser than that on the left cheek, where ointment was being applied—the reverse to that which existed before any treatment was instituted. Then the appearance of acne pustules on the left cheek necessitated a discontinuation of the ointment completely. The menstrual periods during the above treatment were still irregular.

An anterior pituitary gonadotropic factor by hypodermic several times a week was then instituted in addition to an oral placental hormone. Desiccated thyroid, gr. 1 daily, was added empirically. One day, after a month of this treatment, the patient informed me that the hairs on both cheeks were loose and that she had pulled them out completely and very easily. Examination showed that the hairs on both cheeks were almost completely out, with the exception of a few hair roots which were loosely embedded and could easily be pulled out. This was quite a change, since on examination only two days previously the hair growth was quite evident. However, about three weeks after the hairs had fallen out there began a regrowth of hair on the face. These hairs could be picked off very easily by pulling or by tweezer, something which could not be done prior to treatment because of the firmness with which the hair had been embedded. The patient also thought that some of the hairs on her legs had fallen out. It was noteworthy also that the abnormal hairs on the thighs, legs and abdomen could be pulled out very easily in contradistinction to the normal hair which still remained quite firmly embedded.

After about four months of the combined treatment including the pituitary gonadotropic factor, the placental factor was discontinued and the patient continued only with the gonadotropic factor for the next six months. During this time there had occurred a regrowth of hair on the cheeks, but this new hair was not quite as coarse as formerly; some hairs would fall out spontaneously at times, and almost all of the abnormal facial hair could be plucked out very easily by the patient at will. This was true, too, of the superfluous hair situated on the legs, thighs, abdomen, and in the areolar region.

During these nine months the patient had regular menstrual periods, with the exception of the last one which was three weeks overdue. Her breasts definitely had become fuller, her facial appearance more feminine. The patient discontinued treatment; a follow-up could not be made.

Case 4 was 23 and unmarried. Her complaint was that there was a thinning of the scalp hair and dandruff, an overgrowth of hair on the face and body, and a ten-

dency to gain weight very easily if diet was not watched. Her menstruation, which began at about 13 years of age, was always irregular and was preceded for two to three weeks by marked general discomfort and swelling of the breasts. Her libido was normal.

On examination there were noted some bleached hair on the cheeks, a slight amount of hair on the upper lip, many long coarse black hairs in the sternal region, many hairs on the back of the thighs, and some on the arms and legs. Pubic hair was present which extended along the midline to the umbilicus. Axillary hair was present. The breasts were pendulous and contained glandular tissue. The labia minora appeared somewhat hypertrophied; the clitoris was prominent (about 1 cm.). The patient stated that at times her voice would be a real bass, but at other times was not so low. It was, however, gruffer than it had been several years ago.

Her weight was 124 pounds; her height was 60½ inches. Her lower measurement was greater than the upper. The basal metabolic rate was minus 7.2 per cent. Total cholesterol in the fasting blood serum was 193, sugar was 73. Roentgenograms of the skull and osseous system were normal. The patient had a laparotomy two years ago for an appendectomy; both ovaries appeared macroscopically normal.

Local therapy was given for the seborrhea of the scalp. In addition, desiccated thyroid in small doses and a restricted diet were prescribed, and gonadotropic factor was given by hypodermic several times a week. After about two months of treatment the patient noticed that the hair on the legs fell out quite easily, that there was definitely a good-sized area on one leg free from hair, and that the remaining superfluous hair on this leg could be removed by the slightest pull, whereas that on the other leg was as yet firm. The suprapubic hair extending to the umbilicus also could be pulled out very easily, whereas the normal hair on the pubis was much firmer. The hair on the sternum was quite firm at this time.

After further injections, the hair on the sternum loosened and was easily extracted, as was the hair on the patient's cheeks below the normal hair-line. Other large areas free from hair were noted on the outer aspects of the legs. The seborrhea of the scalp had now cleared and the hairs on the head had become quite firm, although at the outset, due to the infection, these fell out very easily. During this period of treatment the patient menstruated regularly for two successive periods.

The above therapy was continued for many months. With it, the hair on the cheeks came out completely, that on the upper lip remained quite firm, and the abnormal hair in other regions fell out in spots or could be pulled out with ease.

However, after several weeks of this status of the hair, there was regrowth of the abnormal hair, but this new hair was finer and quite loosely embedded. The patient admitted that she was well pleased with the outcome of her treatment, since she had been dissatisfied with previous physiotherapy. On one occasion, when she had to wear a low-necked dress (a thing which she had shunned previously because of the hair growth on the midsternum), the sternal hairs had regrown to some extent, yet all she had to do was to apply gentle pulling and thus extract the chest hair. The patient was quite pleased with this accomplishment, and admitted that even though the hairs regrew it was quite an advantage to be able to extract them so easily. Of course attempting to pull these hairs prior to the initiation of the glandular treatment was quite painful and produced inflammatory reaction of the tissue at the hair roots.

For the past year, during treatment, her menstrual periods became more regular, varying in regularity by only a few days.

Five months after discontinuation of therapy the patient stated that although the facial and midsternal hair was regrowing she was quite pleased with the result, since these hairs were very slow in their regrowth, loose, easily extracted. The scalp hair in the fronto-parietal region was thinning out again and the dandruff was again present. Her menstrual periods were quite regular. She had married in the interim.

Case 5, aged 22, presented herself for treatment because of marked obesity, sluggishness, and an overgrowth of hair which had its onset four years previously. The patient's mother and sister also have abnormal hair growth, but not in any way like the patient's. Although the patient was a young girl, her appearance, due to obesity and facial hirsuties, was that of a matron. Her menstrual periods, which had started at the age of 13, were regular, the flow lasting about six days. She was unmarried.

The patient weighed 176 pounds and was 61 inches in height. Her lower measurement was slightly greater than the upper. Her breasts were pendulous, containing much fatty tissue and some glandular tissue. Nuchal and superclavicular fat padding was marked, as were the fat deposits elsewhere over the body.

Examination revealed no evidence of neoplasm. There was a marked hair growth on the chin, the neck, and on each of the outer portions of the upper lip. These hairs were long, black and coarse. Some excess hairs of a finer texture were noted on the cheeks. There was no hair in the sternal region and no marked overgrowth on the legs or thighs. Axillary hair was present. There was some slight extension of pubic hair to the umbilicus. All the abnormal hairs were quite firm when an attempt was made to pluck them. The clitoris was prominent (about 1 cm.).

Roentgenograms of the bony system revealed no apparent abnormality. The sella turcica was bridged. A fasting blood chemistry showed a total cholesterol of 212 mg., sugar 94 mg. Her basal metabolic rate was minus 7.2 per cent.

The patient was placed on a restricted diet and desiccated thyroid; gonadotropic factor was given by hypodermic several times a week.

After about three months of therapy, the patient noted that the hair on her chin, cheeks, and upper lip could be pulled out very easily, and, for the first time, she was free from hair. The regularity of this patient's periods, though, was somewhat disturbed; one period was skipped. On the whole, the patient felt much better. She had reduced 27 pounds in about four months, her appearance was much trimmer, and her social outlook was brighter.

Later, the superfluous hair regrew, as it had in the other patient, on the chin and outer margin of the upper lip, but these were not as coarse and could be pulled out very easily.

Of interest is the fact that prior to treatment, due to her appearance, she could not obtain employment. Since then she has passed a physical examination for a civil service position.

Case 6, aged 18 and unmarried, had not menstruated for the past year. Her periods had begun at the age of 13 years, but had been irregular ever since. At the beginning, her flow was fairly good; subsequently, it became very scanty. Occasionally her breasts would hurt a little before her periods. She experienced general weakness. The patient admitted the existence of a normal libido.

The patient appeared malnourished. Her weight was 107½ pounds, her height was 62 inches. The body proportions were eunuchoid (lower measurement was greater than the upper measurement). Her facial appearance and body contour were more of the masculine type. There was an occasional acne papule on the face and back.

There were a few blonde lanugo hairs on the chin and upper lip. Hair was present on the midsternum (noted by the patient for the past two years), and there were a few long hairs in the areolar region of the mammae. There was abundant hair present in the axillary regions and in the suprapubic region, but the latter extended to the umbilicus. There was also hair present on the posterior aspects of the thighs, legs, sacral region, and some on the forearms. The hair was quite firm and resisted plucking. (The patient admitted that her mother also had some excess hair on her thighs and legs, but none on the abdomen or face.)

The breasts were moderate in size, but the patient stated that they had not in-

creased in size lately. The external genitals appeared normal except for a somewhat prominent clitoris, which was about 1 cm. in size, suggesting a miniature phallus.

Roentgenograms of the skull revealed no abnormality; those of the bony skeleton showed epiphyseal closure of the hand, wrist and elbow. The basal metabolic rate was plus 9.8 per cent. The patient did not coöperate for blood studies.

Anterior pituitary gonadotropic factor was instituted by hypodermic several times a week.

After about a month of therapy the patient had her first menstrual period in a year and flowed for about two days. The abnormal hair at this time was still firm to plucking.

After about two and one-half months of treatment some of the hairs on the anterior chest wall and abdomen were loosening, but most of them were still quite firm.

One month after the above period the patient experienced some drawing down pains in both groins, but no vaginal bleeding occurred.

Two months later, the patient experienced pelvic cramps and stained for three days. During this time the patient took on about four pounds of weight and definitely presented a more feminine facial appearance.

Two months after this last staining the patient had a good vaginal menstrual flow lasting two and one-half days. At this time, after about five months of treatment, the suprapubic hair of the abdomen could be easily plucked although the normal pubic hair was firm. Of interest is the fact that the patient was free from acne for a comparatively longer period of time than before treatment had been instituted.

At the end of six months of this treatment the patient had gained about seven pounds, felt stronger, was quite cheerful and hopeful, and appeared much more feminine.

Case 7 (figures 3 and 4), unmarried, 21½ years old, was a non-obese individual who complained of acne of the face and back, and hirsuties. Her menstruation had started at the age of 11½ years. Although this was irregular at the outset, the periods soon adjusted themselves and became quite regular. Her flow in the past was usually three to four days, but lately was somewhat scantier. Her acne and hirsuties both appeared at the age of 13 years. The patient did not consider herself frigid, but, due to her condition, desire for social intercourse was repressed. The patient says that her father and brother are both extremely hairy.

The patient's facial appearance and body contour tended toward the masculine type. Her entire body surface, including even the dorsal surfaces of her feet and toes, was practically covered with long black hairs about an inch in length. The hirsuties was much more than one sees on the average male, but equivalent to that seen on some hairy males. There was marked hirsuties of the cheeks, chin and upper lip. The pubic escutcheon was heterologous. All the hair was firm and difficult to pluck.

The external genitals appeared normal. The labia minora were prominent and somewhat hypertrophied; the clitoris was not penis-like, but was slightly prominent on retraction of the foreskin. Her voice was feminine.

There was no evidence of neoplasm on clinical study. The fasting blood showed a cholesterol of 220 mg., glucose 75 mg. The basal metabolic rate was plus 4.5 per cent. Her weight was 97½ pounds, height 58 inches.

The patient was given gonadotropic factor by hypodermic injections several times a week.

After two months of treatment the patient found that upon rubbing the legs some of the hair would fall out. The patient admits that this was much more than had ever happened prior to treatment. At this time the hairs on the cheeks and chin could be plucked by me much more easily than originally. The hair on the upper lip was still firm. The acne at times would clear up, only to reappear.

With continuation of the treatment there were noted small areas on the cheeks and the lower two-thirds of the legs that were free from hair.

The patient has now been under treatment for 10 months, but the best that could be done for her so far has been to bring about a more feminine appearance, a loosening

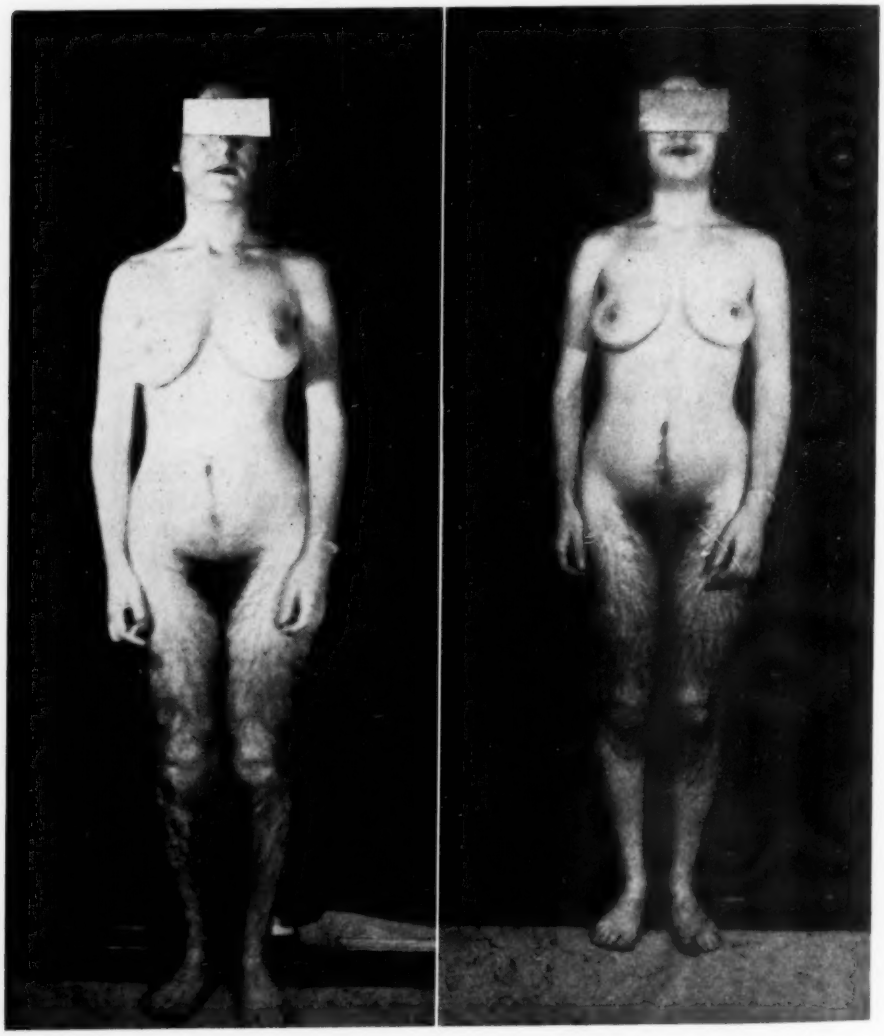

FIG. 3. (Left) *Case 7.* Note marked hirsuties before institution of hormonal therapy.
FIG. 4. (Right) *Case 7.* Note legs after 9 months of hormonal therapy. The hair in parts was plucked quite easily by the patient.

of some of the hair on the cheeks and chin, which could be plucked with more ease than originally, and a loosening of the hair on the lower two-thirds of the legs which the patient was able to pluck almost completely and with ease. The rest of the body hair, including that on the upper lip, is still quite firm to plucking. It was attested by others in the office that the patient's appearance had become more feminine.

In view of the experiences in the other cases treated, I was disappointed in the

slowness of response to the therapy. However, this was one of the worst cases of hirsuties I had ever seen, and any favorable response such as was attained here, as evidenced by the loosening of the hair on the legs and in part on the cheeks and chin, was gratifying.

Later, in this case too, although therapy was still being administered, there was regrowth of hairs on the cheeks and chin, and, although these could be plucked, they resisted plucking much more than did the other cases treated similarly. Also, the periodicity of several of her menstrual periods had been disturbed. She had gained seven and one-half pounds.

At one interval, during the course of treatment, this patient also received, for about one month, large doses of estrogenic hormone, with no radical response.

Case 8, aged 15¾, presented herself for treatment because of her obesity. At the age of nine or so, the patient was said to have a basal metabolic rate of minus 33 per cent and had taken oral thyroid medication. At the age of 13 years, the patient had enuresis and vaginitis, and was treated by "thyroid medication and by injections," with consequent correction of the two conditions. In view of her suspected glandular dyscrasia a repeat basal metabolism was given when she was 15 years old, and a rate of minus 15 per cent was found. The thyroid medication had been continued intermittently to date. Her menstrual periods had started at 12, were fairly regular, except during her injection treatment for vaginitis, and lasted for about three days. The patient was somewhat behind in her school work.

The patient weighed 174 pounds, and her height was 63¾ inches. The lower measurement was greater than the upper. Some pastiness and mild acne of the face were present. There was moderate hypertrichosis of both cheeks, as well as some light-colored hairs on the chin. The breasts were pendulous and contained glandular tissue. An occasional hair was present outside of the areolar region of the mammae. Axillary hair was present. There was a moderate amount of hair on the inner and posterior aspects of the thighs, and in the lumbosacral and gluteal regions. The pubic hair extended up to the umbilicus. There was a slight prominence of the clitoris.

Roentgenograms of wrist, hand, and elbow revealed closure of all epiphyses. The skull and sella turcica were within normal limits. The basal metabolic rate at the first examination was minus 3 per cent. (The patient had been taking three grains of thyroid medication per day.) The patient did not coöperate for blood studies.

A restricted diet was prescribed, desiccated thyroid was continued, and in addition gonadotropic factor by hypodermic injection was given several times a week. After a few weeks of treatment, the patient informed me that the hairs on her face came out very easily when she pulled at or touched them.

With the continuation of the treatment the patient was able to extract easily all the facial hair.

After three months of therapy the patient had lost about 15 pounds and was doing much better in her school work. Her menstrual regularity was not disturbed. The acne disappeared at times, only to reappear. The patient is still under treatment.

Discussion and Comment

In the eight cases presented for consideration no definite neoplastic pathology in the adrenal, ovary or pituitary glands was found on clinical examination. All the patients showed some symptoms of masculinization, as evidenced primarily by hirsuties of the face, trunk and extremities, as by heterologous formation of suprapubic hair, some exaggeration of the size of the clitoris, and, in more than half of the patients, by irregular or scanty menstrual periods. In addition, upon examination, nearly all the cases re-

vealed a reversed body proportion, in that the lower measurement, as measured from the top of the pubic bone to the heel, was greater, to some extent, than the upper measurement, as measured from the pubis to the vertex of the head, a so-called eunuchoid proportion one usually associates with hypogonadism.

With the exception of case 8, where the basal metabolic rate was not indicative, due to the fact that desiccated thyroid had been taken for years because of a suspected thyroid insufficiency, all the cases showed basal metabolic rates which were not significant.

Obesity was a distinct factor in half of the cases; in two of the other cases there was a tendency toward obesity if dietary restrictions were not observed. It is believed by some that obesity is a factor in cases of adrenocortical hyperfunction, for they believe that the adrenal cortex is instrumental in the regulation of fat metabolism and that the cortical hormone has the ability to fix the fats in the tissues.[6] They also believe that weight reduction is difficult in such cases.[7] In my cases, I am not at all certain that such obesity was actually caused by the same glandular derangement as was causing the hirsutism. Furthermore, the customary low blood serum cholesterol value found by these investigators [7] in their cases was not found by me; rather the opposite was found to exist, namely, relatively high total cholesterol values in four cases—two of which were obese, one of which showed a tendency toward obesity, and one case which was non-obese. Also, weight loss could be and was accomplished in those of my series either by dietary restriction alone, or by diet and the addition of desiccated thyroid.

The values for blood sugar taken in six cases tended towards the lower normal values and probably indicated an increased sugar tolerance. In five of the cases where urine tests were done and recorded prior to the onset of hormonal treatment glycosuria was not evident. Hypertension was not a factor in any of these cases.

Prior to the initiation of therapy an attempt was made to judge the firmness with which the hairs were embedded. This was judged by the amount of pull needed in plucking with forceps. Although a somewhat crude method, it gave some idea of the firmness of the hairs. In all cases the existent hair, both in normal and abnormal sites, was embedded quite firmly, and attempts at plucking were difficult and painful to the patient; also, when these hairs were extracted, there usually was produced an inflammatory area at the site of extraction.

Although hormonal therapy did not produce complete eradication of the hirsuties in this series of cases, it nevertheless was noteworthy in that it provoked enough important changes to lead one to believe that it might be a stepping stone towards improved therapy; for it was found that after therapy had been administered for a time a spontaneous falling out of some of the superfluous hairs on the cheeks, chin, parts of the thighs and legs had taken place for the first time in most of the cases. In addition, in all of the

cases, at some time during hormonal treatment, the superfluous hair which had not fallen out spontaneously began showing a loosening at the roots. This occurred in the hirsute regions of the cheeks, chin, mid-sternum, abdomen, and parts of the thighs and legs. It was found then that when such loose hair was gently pulled, or when the hirsute area was gently rubbed, there was a falling out of the hair. This loosening or spontaneous falling out of hair did not, however, occur in all hirsute areas at the same time; nor did it follow a definite pattern. For example, in some, there first appeared small denuded areas on the parts of the thighs, with the superfluous hair on the rest of the thighs and the superfluous hair on the other parts of the body remaining firm and not responding until further therapy had been administered. In others, the hair on the cheeks loosened or fell out first, whereas the rest of the superfluous body hair remained firm until further therapy had been administered. On the whole it was found that the superfluous hair on the upper lip was most resistant to therapy, even though the superfluous hair on the cheeks and chin responded readily. In all cases, with but one exception (case 7), most of the hirsute areas showed some response, in varying degrees, so that even where some of the superfluous hair did not actually fall out, it at least loosened at the roots and thus lent itself to easy extraction. Even in the exception, the worst case of hirsuties the writer has ever seen (case 7), where the abnormal hair was more resistant to treatment than it was in the other cases, there was eventually a loosening of some of the abnormal hair on the cheeks, chin, and especially on the legs and forearms, which could be plucked more easily.

It is of interest that in several of the patients in this series, there was a familial tendency to superfluous hair formation. However, in spite of this apparent hereditary factor, there was the same response to hormonal treatment in these cases as there was in those presenting no hereditary tendency.

Such good effects on hirsuties as were obtained were no doubt very gratifying. I found later, though, that this promising state did not remain entirely unchanged, for soon a change took place and the excellent results were comparatively short-lived. Within a period ranging from several weeks to several months, there began a regrowth. With this regrowth, though, a gratifying thing occurred; the new hair no longer appeared in its original stubborn or coarse state, but rather it now showed up with a lighter color and finer texture, and in a more loosely rooted state so that it could be plucked with ease without causing pain or inflammation. (These changes in hirsute females were in line with the observations noted by A. D. K. Peters.[8])

While all of these changes were taking place in the hirsute areas, it was significant that the normal hair did not fall out, nor did it ever loosen. In one case (case 4) where a sparseness of hair was evidenced in the frontoparietal regions of the scalp, and with it a case of seborrhea (for which local medication was used), there even occurred a regrowth of firm hair in that

region during hormonal treatment. It is true, though, that after hormonal treatment had been discontinued for three months, there was a regression and some of this hair again fell out and the area again was somewhat sparse.

Of significance, too, were the other accompanying changes which took place during the course of hormonal treatment. It was noted that in addition to changes in the hirsutism the menstrual irregularity tended toward correction in some of the patients, and in one case (case 6) several periods occurred after an amenorrhea of one year. It is true too, however, that in a few, where the menstrual periodicity had been apparently normal, a temporary disturbance then occurred, possibly due to treatment. Later though, with a subsequent check-up after therapy had been discontinued, it was found to have once more reverted to the normal. In all cases, though, whether the menstrual periodicity had been regulated or disturbed during hormonal treatment, the above-mentioned effects of falling out and loosening of the superfluous hair took place.

In addition, the general psychic outlook of most of the patients in this series was greatly improved, and a certain feminizing effect was reflected in the facial appearance and demeanor of most of them (as indicated in the case reports) after treatments had been in progress for a time.

With regard to the therapy administered, judging from my series of cases, which I realize is small, I found the following:

Of the four cases in which estrone by inunction was given it was found that very few significant effects could be attained. Of course, it is possible that the dosage of 1,000 I.U. in each gram of ointment was inadequate. The effects which were noted, though, were that after inunction a slight bleaching of the hair seemed to occur, and, at times, although the roots remained, there was a breaking off from the surface of some of the coarse hairs at the sites of application.

In one case where a combined therapy of inunction and injection of estrone was given it was found that, in addition to bleaching effects, there was produced some loosening and falling out of hair on the thighs, rather than just a breaking off of hair from the surface.

In other cases, where in addition to the local and hypodermic estrogenic therapy, oral administration of emmenin was given in an attempt to provoke ovarian stimulation, some striking results were attained. Emmenin, which is a product of the chorionic villi of the placenta having some gonadotropic-like effects in addition to its estrogenic effects and requiring the presence of ovarian tissue for its action, was given in an attempt to provoke ovarian stimulation. In one case (case 2) after administrations of emmenin, this combination therapy produced quite striking results, so that where shaving of the hair of the face had been necessary, now the facial hair either fell out or was loosened so that it could be plucked easily, and shaving became unnecessary. (It is unknown what the state of this patient was after she had discontinued therapy, for a follow-up was impossible.) In another case (case 3) where inunction and hypodermics of estrone produced

no results at all, the addition of emmenin provoked a response, and facial hair then began to loosen and become more sparse.

As can be seen from the effects listed above, estrogenic products had different effects on different individuals in this series; in some, injection or inunction of estrone produced good results; in others, it produced no effects, and only after emmenin was added was there some response to treatment. It is difficult to decide, however, even though emmenin did provoke a good response, whether this product was the initiating factor setting up the response, or whether it merely contributed in furthering the response already initiated by estrogenic therapy. It can be seen that evaluation of each product is difficult, particularly because I had so few cases with which to work.

It is possible, however, that the gonadotropic-like properties of emmenin may have been responsible for some of the good responses. I believe this to be likely in view of the fact that when a gonadotropic factor of the anterior pituitary gland was used and administered alone, in some of the other cases, decided effects on the hirsuties were evident in a short time. This occurred in all of the five or six cases where hypodermic injections of gonadotropic factor were given. In all it was found that this gonadotropic product could be counted upon to produce results no different from the ones obtained with estrogenic hormone, but that it could be relied upon to produce these results more definitely, more quickly, more consistently and more effectively.

What the underlying physiologic basis for the effect of this anterior pituitary gonadotropic factor on the hirsuties was, is not clear, but one is tempted to speculate that its action may have been by direct effect on the ovary. At present it is hard to find the reason why estrone, which is a product of the ovary, should not produce the same striking results as the gonadotropic factor, which apparently stimulates the ovary directly and produces female sex hormone or estrone. One would expect the substitution of the finished product of the ovary, namely estrone, to accomplish the same end result as the female sex hormone which is produced by the ovary itself through gonadotropic stimulation. Of course there is the possibility that some other physiologic action may be taking place other than the supposed action through the ovary. Be that as it may, however, it is not within the scope of this paper, at the present time, to delve into a theoretical discussion; nor is it justifiable to attempt at this time to make dogmatic statements without more definite proof in a larger series of cases. Suffice it to say that some therapeutic approach to the problem of hirsuties has been attempted which it is hoped will aid in stimulating further study of this problem.

Summary and Conclusion

An attempt was made to offer a more basic form of therapy to hirsute females who, I presume, had a glandular derangement in the form of a hyperfunctioning of the adrenal cortex and a disturbance of the ovary, with-

out clinical evidences of any apparent neoplasm in these glands. This study was comprised of a group of eight females, from 15 to 23 years of age, who showed hirsutism in degrees, varying from slight facial hair and body hair growth to such marked hair growth that it required shaving, and who showed, in addition, some exaggeration of the clitoris and some menstrual irregularities.

These cases were submitted to various forms of estrogenic and gonadotropic therapy, administered orally, hypodermically, and by inunction. The following responses were noted:

Inunction on the face with estrogenic hormone, given in three cases, produced a very slight bleaching effect in the area where the ointment had been applied, and at times a breaking off from the surface of some of the coarse hairs, with the roots remaining. It is possible that the dosage used in these cases was insufficient. No such effects were noted in areas where the ointment was not used.

A combined therapy of inunction and injection of estrone, given in one case, produced not only the same bleaching effects, and a breaking off of hairs from the surface of the face where the ointment had been applied, but in addition there was produced an actual loosening and falling out of some hair on the thighs.

Oral administration of a placental extract, emmenin, containing not only estrogenic, but also gonadotropic-like properties, was given in two cases, in addition to local and hypodermic estrogenic therapy. With this addition of emmenin to the therapy, in one case, even where previous estrone therapy had produced no apparent result, there was now provoked a loosening and falling out of some of the facial hair. In another case, there was provoked a falling out and loosening of the hair so that it could be plucked easily, thus eliminating the necessity for shaving. It was quite likely that the apparent good effect of this product was due to the gonadotropic-like property it contained, especially in view of the subsequent success attained with an anterior pituitary gonadotropic hormone.

Hypodermic administrations of a gonadotropic anterior pituitary hormone alone provoked definite, quick responses in the majority of the cases. With this product the effects on the hirsuties were the same as when estrogenic hormone had been used; there was the same falling out and loosening of superfluous hair, but this product was more satisfactory and more dependable in that it was more consistently efficacious and could be counted upon to act more readily and more rapidly.

Other hair, in the normal sites, did not, throughout treatment with any of these products, loosen or fall out—it remained, as before, firmly embedded and showed no change in texture. In fact, in one case where there was a seborrhea of the scalp and the hair of the head was thin and had fallen out, a regrowth and firmness of the hair occurred during the period of hormonal and local treatment.

Loosening and falling out of superfluous hair were produced in a varying degree with hormonal treatment in all of these cases. Later though, a regrowth occurred. This regrowth, however, was of a lighter color and finer texture, and was more loosely embedded, so that it could be easily extracted.

At this time it is difficult to predict what the status of the hair will be in the future after there have been a series of depilations.

Even with incomplete results, the present modification in the hirsuties has caused a modification in the psychologic outlook of these patients as reflected in attitude, appearance and behavior.

Changes also took place in menstrual periodicity. Usually, where the menstrual rhythm was irregular, it tended to correct itself during hormonal treatment. In a few, though, where there had been a regular periodic menstrual rhythm prior to treatment, there occurred a disturbance of this rhythm during treatment. This, however, on subsequent check-up in two cases after treatment had been discontinued, was found to have corrected itself.

I am well aware of the smallness of the number of cases included in this series, of the incompleteness of this study, and of the short-comings of the therapy; I am also aware of the difficulty in evaluating the individual hormonal products used here. Nevertheless, I have presented this paper at this time as a preliminary report, in the hope that it might be a stepping-stone towards further clarification of such types of cases, and that it may aid in the arrival of a more exact basic therapy.

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PSEUDO-MEGACOLON *

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I

Megacolon is recognized, either clinically by the severe constipation it causes; or roentgenologically, by the increase in size and capacity of the colon. It is noteworthy, however, that extreme enlargement, as revealed by opaque enema, may not be found again on subsequent examinations [4, 13]; such instances are due to acute intestinal atony, which occurs, for example, in renal colic, and may be produced experimentally in man by distention of the renal pelvis.[13] Clinically, this transient disturbance has been known for a long time.[11] It does not show itself by definite symptoms, since the colon regains normal tone in the course of a day or two; moreover, the intensity of the primary colicky pain outweighs any other associated discomfort.

From this acute reflex disorder the condition hereafter reported differs by reason of its chronicity and its entirely different roentgenologic features. It was observed in two groups of patients: in the first (seven persons), as a pronounced anomaly which had developed in early childhood; in the second (22 persons), as a less characteristic disturbance beginning in the third or fourth decade.

The patients of the more illustrative first group (four male, three female; five Europeans, two Arabs) stated that they had "always" been severely constipated; in four instances, the parents asserted that constipation had actually begun when the patients were less than two years old. Ever since, spontaneous evacuation would occur only once in six, eight, or even eleven days. Except for a sensation of moderate heaviness and of a "hazy head" towards the end of this period, there were no other definite clinical symptoms. Every imaginable mode of treatment had been attempted, including diets, drugs, massage, physiotherapy, and "cures" of all kinds. Purgatives, after being taken for many years, finally failed to act, whereupon soap enemata were resorted to. The patients, who were about 20 years of age when first seen by us, now sought advice because they felt that the trouble was increasing; but close questioning elicited the fact that spontaneous calls to stool were as frequent (or infrequent) as in previous years; only the response to cathartics and enemata had grown weaker. All the patients were rather slender, though not undernourished; they did not eat much for fear of distention. Otherwise they did not belong to any common constitutional or emotional type.

In patients of the second group, the complaints were less marked but essentially similar. Constipation had developed in the thirties. Eighteen

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of the 22 patients were women in whom sundry diseases coexisted, such as old fibrous lesions in the lungs, infections of the biliary tract, the bladder, or renal pelvis, and the like.

In the patients of the first group, physical examinations did not reveal anything of significance. The abdomen was normal on palpation; there was no pain; and there were no signs of infection, nervous disease, or endocrine disorder. But the roentgen findings were almost identical in these seven cases. Opaque enema showed a perfectly normal colon; the opaque medium was evacuated spontaneously. Barium given by the mouth passed through

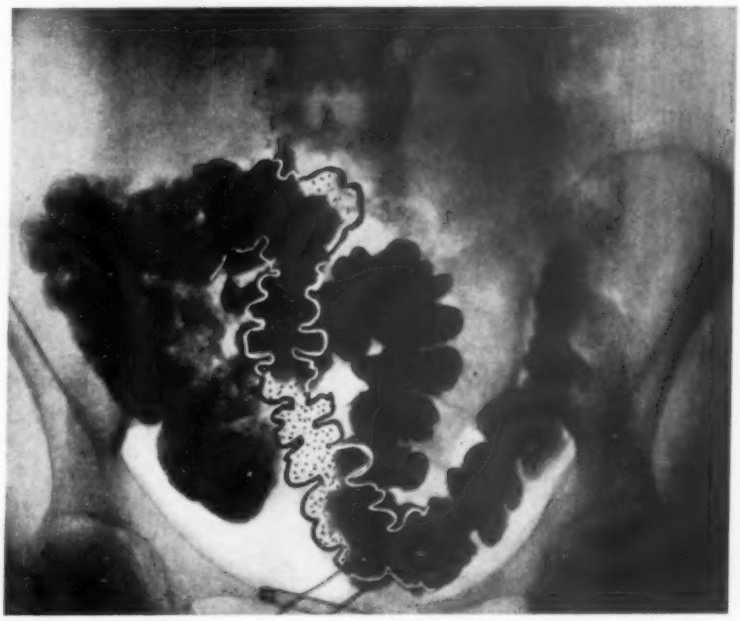

FIG. 1. Radiographs taken in the upright position at 6 feet (no distortion) under identical conditions, 5 and 5½ days after barium meal. The drawn contours indicate the position of the colon as traced from the second radiograph (5½ days). "Isomorphic" haustration. Opaque contents have not moved beyond splenic flexure. Serpentine mobility of transverse colon. A girl 21 yrs. old.

the stomach and small intestines normally; and 24 hours later, the ascending and transverse colons were filled. The haustration of the latter was particularly regular and uniform (isomorphic). There were no kinks or fixations. But, during the subsequent six or seven days, the opaque contents did not move beyond the splenic flexure. In two patients, serpentine movements of the entire transverse colon were definite during this period (figure 1), and haustral peristalsis was quite active. Within about 20 hours before spontaneous evacuation, particles of barium about one half the size of a haustrum were seen in the descending colon. Then, suddenly, the transverse colon was found free of barium, and the descending and sigmoid loops filled

with it. Defecation occurred a few hours later; the fecal material was rather dry, but not especially hard. Neither on palpation, proctoscopy, nor on roentgen examination, was any anomaly found in the rectum. The condition has nothing in common with dyschezia but the presence of constipation.

Very marked in the first group, these roentgen findings were less characteristic in the second; but it was common to both that the progress of barium was stopped, entirely or chiefly, at the splenic flexure; that the haus-

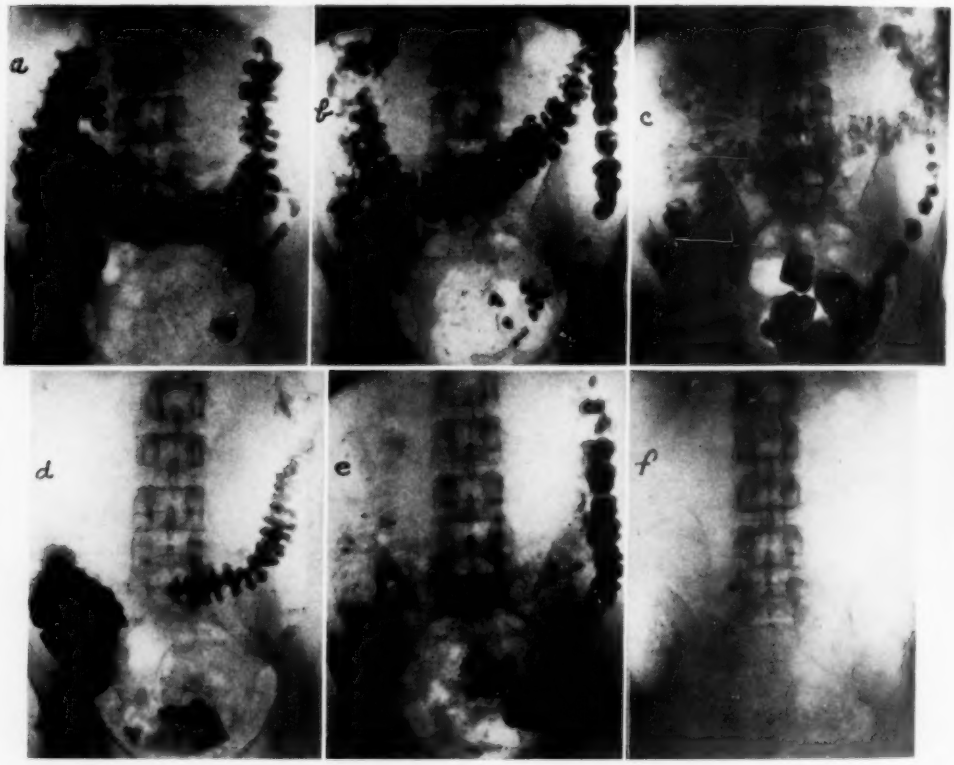

FIG. 2. Upper row: Colon 5 days (*a*), 9 days (*b*), and 9½ days (*c*) after barium meal. In (*c*) mass peristalsis has emptied the transverse colon. Lower row: Same patient three weeks after termination of pituitrin treatment. Colon 7 hours (*d*), 24 hours (*e*), and 48 hours (*f*) after barium meal. Mass peristalsis occurred between 7 and 24 hours after opaque meal. A merchant aged 24 yrs.

tration of the transverse colon was conspicuously regular; and that there was no retention in other parts of the colon, except for the slight physiological stasis which occurs normally in the cecum after the transverse colon has emptied itself.[14]

II

In man, various influences modify colonic mechanics. Mental [2, 16] and climatic factors may be interlinked with the results of individual habits [2] and common customs.[14] Although a barium meal passes through the digestive

tract in a way quite different from the passage of normal food,[1] there is, at present, no better method of observation than roentgen examination, which shows that pendulum, rhythmic and stripping movements are often superimposed, corresponding to the simultaneous processes of absorption and transport. Individual and accidental variations may modify the appearances. In this variety, one mechanism stands out, namely, the caudad motion of the contents from the transverse into the descending colon by means of mass peristalsis. Preceded by a sudden disappearance of the haustra,[2, 8] mass peristalsis appears as a stripping tonic contraction[5, 8, 14] which, having its *point d'appui*[2] either above the cecum or at the hepatic flexure,[2, 14] constricts and stretches the transverse colon within about three seconds. The stripping or milking movement travels rapidly caudad, forcing the contents onward into the descending colon (figure 3), until activity ceases when the

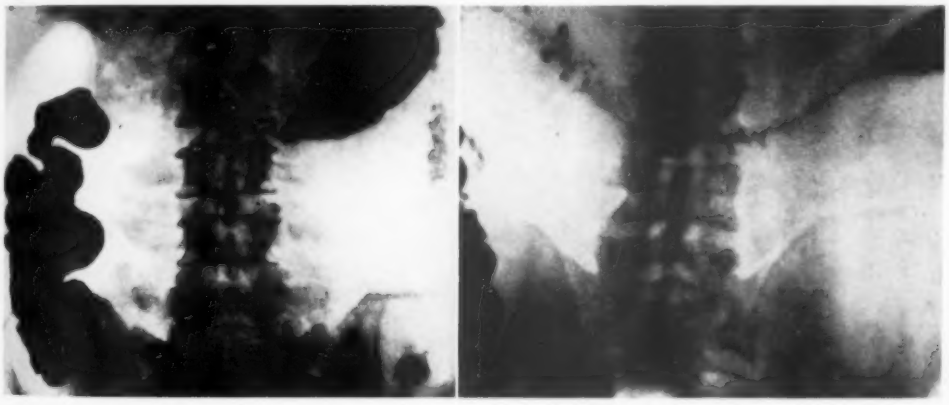

FIG. 3. Normal mass peristalsis. Radiographs taken during the movement. By a stripping contraction, the contents of the transverse colon, spindle-shaped, are driven into the descending colon.

contraction reaches the splenic flexure. This "systolic" movement is normally preceded by a very much slower "diastolic" relaxation of the transverse colon[14] which, after having been completely filled from proximad, loses in tone and peristaltic activity very gradually in the course of from seven to 24 hours; this produces the downward curving and the isomorphic haustration characteristic of the position of rest.[14] If mass peristalsis sets in before this relaxation is complete, it empties parts only of the transverse colon; obviously, the "systolic" contraction is less effective when the "diastolic" slackening is either incomplete, defective, or impaired. This mechanism underlies various types of hypertonic and hyperkinetic constipation.

In the disorder here discussed, however, the transverse colon relaxed normally, and remained relaxed during an abnormally long period; mass movements, when they finally occurred, were normal in appearance and mechanical effect. Nothing, in fact, was wrong with the colon except for the ex-

treme prolongation of the interval between relaxation of its transverse portion and onset of mass peristalsis.

III

Mass movements identical with the spontaneous ones can be induced experimentally in man by injection of 5–10 Voegtlin units of postpituitary extracts. Contraction occurs about 50 minutes after hypodermic injection, provided the transverse colon is relaxed.[12] In the patients here discussed, injection of pituitrin invariably induced mass peristalsis after this interval. Injection of simple saline solution (the nature of which was unknown to the patients), as well as of atropin and prostigmine, did not elicit any movements. Accordingly, the patients were given three injections weekly of 1 c.c. of pituitrin over periods of three to four weeks, with the result that constipation ceased immediately and normal bowel movements were maintained at least for several months after termination of the treatment. Recurrence was observed in three patients, but subsided after repetition of the series of injections. Four of the patients were observed during periods of from two to four years; in two of them, constipation did not recur at all after the first four injections; in one, there was one recurrence; and in the fourth, treatment has to be resumed about once a year. All sorts of lubricants and cathartics were entirely ineffective in these cases. No special diet was recommended. Enemas were forbidden, but two patients confessed that they resorted to them once in a while.

IV

Constipation occurs in pituitary disorders,[6, 7, 10] where it may be associated with enlargement of the entire colon or parts of it [10]; it is also not uncommon when pituitary function is physiologically modified, e.g., in early pregnancy, before the uterus grows larger and presses upon the colon; and at the beginning of the climacteric. In these cases, as well as in acromegaly, we have occasionally found a general slowing down of colonic activity, but no isolated deficiency of mass peristalsis. The patients of our first group did not show clinical signs of pituitary disorder, although the disease had lasted some 20 years. Slight degrees of pituitary dysfunction, however, cannot always be ascertained by present methods, as normal variations merge with abnormalities of the endocrine formula. As to the therapeutic effect of postpituitary extracts, a clinician may be quoted who used to teach that, if a man was starved, and he put on weight when he was fed with steaks, this result did not prove beyond doubt that the starvation was necessarily due to a lack of steak-hormone in the blood. A correlation between normal or disordered mass peristalsis and the pituitary body is not established.

It is held that in Hirschsprung's disease the thickening of the colonic walls is the outcome of a primary disturbance of innervation.[2, 9] In spite of excessive stasis and definite reflex disorder of long duration, there was no colonic enlargement in our cases. The general roentgenologic aspect, the spontaneous occurrence of effective mass movements, and the results of pi-

tuitrin injections show that the intestinal walls had remained intact. The disturbance was not due to spasms, for it was not relieved by atropin and other spasmolytics; nor was it produced by purely mental factors, as injections other than of pituitrin failed to affect it. There was no abnormal position of the colon (which is very rarely responsible for constipation anyway). The absence of systemic symptoms in colonic stasis of such protracted duration does not support the old hypothesis of colonic autointoxication.

Exceedingly little is known about the correlations between normal and pathological motility on the one hand, and the processes of digestion, the vegetative system, the mind, and sundry extraneous factors on the other. Since these influences combine and overlap in the individual case, the notion that constipation is either essentially atonic or essentially spastic does not agree with this variability, nor with the wide individual and accidental variations observed roentgenologically. In this multiformity two well defined disturbances stand out: first, retention confined to the rectum, dyschezia; and, second, the disease above reported which is characterized by retardation of mass peristalsis, as is dyschezia by delayed contraction of the rectum. It is likely that from the study of such distinct disorders more information will be obtained about the normal motor physiology of the colon in man.

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THE POPULARITY OF THE EWALD-BOAS TEST MEAL; REASONS FOR ITS SURVIVAL *

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In spite of all the criticisms directed against the orthodox method of gastric analysis involving the use of a carbohydrate test meal, it is still a favorite with the medical profession. Many clinicians are satisfied with only minor modifications. At the Mayo Clinic arrowroot biscuits and water are still used as the routine test meal. Objections directed against the single aspiration method and the Ewald-Boas test meal are, from a scientific point of view, well-founded, yet the advocates of this time-honored method of gastric analysis after administration of a meal of bread, crackers, biscuits or cereal, refuse to yield ground and maintain that for clinical purposes it is quite satisfactory, and in some respects superior to the newer ones. In 1925 Boas [1] reviewed arguments pro and con raised during the 40 years that the test meal, introduced by him in 1885, had been in use. He came to the conclusion that it still remained best for everyday use in clinic and in private practice. Since then there have been very few articles recommending it. In a presentation before the American Gastroenterological Association at its meeting in 1932, one of us [2] (Z. S. in collaboration with Drs. J. A. Marks and J. L. Kantor) stated that "our feeling is that for practical purposes it matters little what is used for a test meal or how many extractions are made. . . . It is only the exceptional case that will give low figures with one method and high ones with another." We are in full accord with the views promulgated by Eusterman [3] in his book, and readers are referred to it for a thorough and objective discussion of the question.

It is not the object of this communication to go into detailed discussion of the physiology of gastric secretion, the numerous types of test meal suggested, and methods of procedure advocated. An idea as to the variety of test meals used can be gained from the several references given below.

Boas [1] states that the earlier investigators (Leube, Riegel, Jaworski and Gluzinski) used egg albumin or beefsteak.

Isaak-Krieger [4] enumerates the following test meals, suggested by various authors:

Ehrenreich—milk, bread and other foods.
Skaller—soup, flavored with "maggi" (a concentrate used as a condiment).
Rehfuss—oatmeal gruel.
Schwartz and Seldine—bouillon.
Weitz—bouillon with sugar-color added.

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Galewski—tea.
Leschke—kimmel-flavored alcohol.
Ehrmann—dilute alcohol, 5 per cent.
Rothchild—" plasmon " solution (a protein drink).
Vandorfy—water.

Petrowych [5] quotes Talma as recommending the use of a solution of Liebig's meat extract. Also:

Kauber—3 per cent sugar solution.
Gorschkov—fish soup.
Leporski—white cabbage juice.
Katch—solution of caffein.
Kaiser—a solution of " Maggi-wuerfel " (a bouillon cube).

Simnitski [6] suggested the use of a double test meal consisting of 200 c.c. of beef bouillon, giving one after fasting contents were aspirated, removing fractions every 15 minutes, emptying the stomach after one hour, then administering a second meal of 200 c.c. of beef bouillon and aspirating four more fractions at intervals of 15 minutes.

Fleckel [7] advises the same procedure, using Boas-Ewald test meals.

Makarewitsch [8] used bouillon of definite concentration, colored red.

Vandorfy [9] suggests that a Boas-Ewald test meal be given and aspirated in 45 minutes, and that seven days later two similar test meals be given at 45 minute intervals, and the stomach aspirated 45 minutes after the second meal.

Recently, acidity reduction tests were suggested as a part of the general study of gastric secretion.[10] This involves the introduction of decinormal HCl into the stomach and plotting a curve of reduction of acidity by fractional aspiration.

Many writers [11] consider the single aspiration as giving incomplete data, whereas others [12] consider the results obtained by the fractional method erroneous and misleading.

In evaluating the objections raised to the single aspiration method and to the use of a carbohydrate meal for the stimulation of gastric secretion, one must admit the crudity of the procedure, the frequent inaccuracies, and that at times the results obtained are unreliable. As stated above, it is for many reasons entirely unsatisfactory in accurate, scientific investigations. This was admitted by Boas and by other advocates of his method. For that matter, many of the modifications offered are also not free from objectionable features.

Recently Wilhelmj, reviewing the subject,[13] recommends the following changes in technic:

(1) The use of a more suitable test meal such as a specially prepared Liebig's extract solution. (2) Determination of the total secretions entering the stomach by adding phenol red to the test meal and determining the percentage of the original

meal left in each gastric sample. (3) Titration of the total acid in the sample, using an indicator which is free from the errors inherent in the use of phenolphthalein. (4) The separation of the total secretions entering the stomach into the fluid of the acid secretion and the fluid of the non-acid secretions. (5) Determination of the acidity of the total fluid secretions entering the stomach. (6) Discarding the determination of what are known as "free" and "combined" acid fractions.

We were considering the introduction of the above procedure in our clinic. It would involve the use of a solution of Liebig's extracts for the test meal, the employment of the fractional method in all cases, the use of brom-thymol instead of phenolphthalein as an indicator, and the addition of phenol red to the meal for the quantitative colorimetric estimation of gastric secretion and evacuation. However, before deciding on any change, we analysed our material for the past eight years. It was necessary that the advantages of the method proposed be sufficient to make up for the added discomfort to the patient and for the increased amount of work in the laboratory.

Material and Methods

The material presented in this communication was obtained from one of the gastrointestinal clinics at the New York Post-Graduate Hospital.

We have been using in our clinic the following as a routine:

Five Uneeda biscuits and 400 c.c. of water were the test meal. Fasting contents were aspirated only when hypersecretion was suspected. Aspiration was done with a large tube (34 F. or 36 F.) 45–50 minutes after ingestion of the meal. If the contents were negative to Congo red, a Levin tube was passed and several fractions aspirated at 15 minute intervals.

A histamine test was done one or two weeks later when no free HCl was found by the fractional method, using Toepfer's indicator. In a number of cases, we also administered hypodermically 4 c.c. of a 1 per cent solution of neutral red, and observed the color of the fractions obtained. Those specimens which showed no coloration were acidified with HCl.

Results

In all, 2,153 gastric analyses by the single aspiration method were done. (Table 1.) There was ample free HCl in 1,909 instances, leaving 244

Table I

Incidence of Achlorhydria in 2,153 Cases as Determined by Single Aspiration after a Carbohydrate Meal

Free HCl present in	1,909 cases	88.7%
Free HCl absent in	244 cases	11.3%
Total	2,153 cases	100%

achlorhydrias (11.3 per cent). There were proportionately more cases of achlorhydria in women than in men. (Table 2.) About one-third of

TABLE II

Sex Distribution. Incidence of Achlorhydria as Determined by Single Aspiration after a Carbohydrate Meal

Males (1,087 cases)		
Free HCl present in	974 cases	89.6%
Free HCl absent in	113 cases	10.4%
Total	1,087 cases	100%
Females (1,066 cases)		
Free HCl present in	934 cases	87.6%
Free HCl absent in	132 cases	12.4%
Total	1,066 cases	100%

the achlorhydria cases subjected to the fractional method were found to be able to secrete HCl under the same stimulus (Uneeda biscuits), leaving only 7.5 per cent in the achlorhydric group. (Table 3.) Sixty-four cases had

TABLE III

Free HCl Absent on Single Aspiration, Free HCl Present by Fractional Method

Total number of cases examined	118	
Achlorhydria by both methods	79 cases	67%
Achlorhydria in single aspiration; free HCl present by the fractional method in	39 cases	33%
Total	118 cases	100%

histamine by hypodermic injection. Of these, 15 had free HCl, which reduced this percentage to 5.6 per cent. (Table 4.) Twenty-six patients had

TABLE IV

Results of Histamine Stimulation in 64 Cases Found Achlorhydric by the Fractional Method

Free HCl present in	15 cases	23.4%
Free HCl absent in	49 cases	76.6%
Total	64 cases	100%

4 c.c. of a 1 per cent solution of neutral red injected simultaneously with the histamine. All cases with free HCl also excreted the dye into the stomach. (Table 5.) It is interesting to note that in five cases there was neutral red

TABLE V

Neutral Red Excretion into the Stomach. Histamine Stimulation

Total cases receiving neutral red and histamine	26
Free HCl and neutral red present	10
Free HCl and neutral red absent	11
Free HCl absent, neutral red present	5

present in the gastric contents, where there was no free HCl after repeated stimulation with histamine. Thus, in about half the number of cases which showed achlorhydria by the single aspiration, no HCl was found by the other methods used.

In none of our cases was there any abnormality of the blood picture found during periods ranging from one to three years. Each of the achlorhydric cases had several complete blood examinations, including hemoglobin estimation, counts, and morphological study of the erythrocytes.

Discussion

Considering the fact that 89 per cent of all cases in which a gastric analysis was done showed free HCl in sufficient concentration by a single aspiration, using a carbohydrate meal, it seems to us that it is unnecessary to subject patients to the more complicated procedure of fractional aspirations. It would, from the clinical point of view, serve no useful purpose in nine cases out of ten. The tenth case may be reserved for more elaborate study. It is fairly generally conceded that the determination of the degree of gastric acidity is not of great diagnostic significance. Ehrmann[15] contends that exact determination of degrees of gastric acidity is unnecessary and unimportant. It suffices to judge, by the intensity of the bluish discoloration of the Congo red paper, whether the gastric contents contain a large, normal, low amount of free HCl, or none at all. Hyperchlorhydria or achlorhydria are not pathognomonic of any organic disease of the gastrointestinal tract. Indeed, either one is consistent with perfect health. Carlson[14] states that in normal persons gastric secretion may vary from hyperchlorhydria down to complete anacidity.

The different curves obtained by the fractional method, which were at one time considered peculiar for various pathological conditions, are no longer so regarded. Though some clinicians have entirely given up test meals as aids in diagnosis, they are, we believe, a small minority. Gastric analysis is so commonly used, because a great deal of information is gained by even the simplest test. At times gastric analysis clinches a doubtful diagnosis. Not infrequently the presence of ample free HCl makes the diagnosis of primary anemia quite questionable. Whereas carcinoma of the stomach may occur with a fair amount of free HCl, such an occurrence is nevertheless the exception. When the diagnosis is in doubt and the differentiation between chronic ulcer and malignancy comes into question, the finding of hyperchlorhydria will favor the former. Discovery of an unsuspected achlorhydria serves as an indication to modify the diet and the general management of a case. Hurst[16] considers achlorhydria as a precursor to gastric carcinoma. Bloomfield and his associates,[17] realizing the possibility of achlorhydria being a predisposing factor to the development of gastric carcinoma or pernicious anemia, started several years ago an anacidity clinic with the object of following these cases up for a number of years. Kahn[18] recently pointed out that, having examined 840 records of cases of pernicious anemia, there were no cases of peptic ulcer found. Most of the cases were proved to have achlorhydria, and Kahn assumes that all of them were achlorhydric. Thus, one can hardly expect a gastric or duodenal ulcer to develop in a patient showing achlorhydria. The lack of HCl in proved cases of gastric ulcer is recognized as a rarity and is probably due to a secondary gastritis.

Summary and Conclusions

Gastric analysis is a worth-while procedure in all cases presenting any aberration of the digestive functions.

The single aspiration method and the carbohydrate test meal are satisfactory and give sufficient information in 90 per cent of cases.

The remaining 10 per cent may be further studied by the fractional method, using histamine, neutral red or any other method for the differentiation between true and false achlorhydria.

We believe that the procedure advocated by Wilhelmj is not applicable for routine gastrointestinal examinations in the clinic or in private practice. The greater accuracy and scientific value of the method proposed is, in the predominating majority of cases, far outweighed by discomfort to the patient and by the additional laboratory work, without adding anything of clinical value. Because of the considerable labor involved in this procedure, the tendency on the part of the clinician, if the precise method were advocated as a recognized routine for general adoption, would be to omit the test altogether. Thus, a valuable aid in the management of gastrointestinal disorders might be neglected and fall into disuse.

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SOME OBSERVATIONS ON THE PERSISTENCE OF THE BACHMAN SKIN TEST AND OF EOSINOPHILIA AFTER RECOVERY FROM TRICHINOSIS *

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The value of the skin test in the diagnosis of trichinosis has now become definitely established through the researches of a number of investigators although the discovery of this procedure took place only 10 years ago. Bachman,[1] in 1928, showed that specific precipitin and skin tests could be obtained in experimental trichinella infections in laboratory animals. In 1932 his work was confirmed by Augustine and Theiler,[2] who first used the skin test as an aid to the diagnosis of trichinosis in human subjects. During the past eight years the skin test has been used in the investigation of a number of epidemics of the disease and in studies of sporadic cases as they have appeared in large hospitals. These reports [3, 4, 7, 10, 11, 12] indicate that the test is positive in from 70 per cent to 100 per cent of cases, and that it is of definite value as a diagnostic test.

Two distinct types of skin reaction to the Bachman antigen have been observed in trichinosis. The reaction peculiar to the earliest cases has been described by Spink [3] as delayed in type. He has recorded 5 cases in a series of 60, all but one with positive skin tests, who showed this delayed type of reaction. It was characterized by an initial flare which subsided quickly; then in 12 to 24 hours, at the site of injection of the antigen, there appeared a reddened, slightly edematous area from 1 to 3 cm. in diameter. This reaction, observed only in very early cases, reached a maximum within 18 to 24 hours and gradually subsided over a period of days. By the seventeenth day of the disease these five cases showed the more usual immediate type of reaction, characterized by a wheal and surrounding erythema which appears in about five minutes and is maximal within an hour. It is the persistence of ability to show this immediate type of skin reaction with which this paper is concerned.

There is but little available information regarding the length of time that eosinophilia and a positive skin test persist after recovery.

Augustine and Theiler [2] noted in their first publication that there was no marked difference in the intensity of the reaction elicited by the skin test in subjects early in the disease or in those obtained six months after the infection.

McCoy, Miller and Friedlander [4] tested 39 persons from three to twenty-

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two months after infection, of whom 49 per cent reacted to a 1 : 10,000 dilution of the antigen, and an additional 31 per cent reacted to a 1 : 500 dilution. Another group of 13 persons had been ill with trichinosis 3½ to 7½ years previous to the test. Of this group 23 per cent were positive to the 1 : 10,000 dilution and an additional 39 per cent reacted to the 1 : 500 dilution. Theiler, Augustine and Spink [5] reported the testing of five individuals who had been ill with known trichinosis from five to nine years previously. Two cases, nine and seven years later, showed negative skin reaction. The others, 7, 5½, and 5 years later were positive. A 1 : 10,000 dilution of the antigen was used. Sobel [6] applied the test to five children with known past infections. One child reacted to the 1 : 10,000 dilution three years and eight months after the infection, another four months after the infection; a third child after 3½ years reacted to a 1 : 500 dilution but was negative to the 1 : 10,000. The other two, after 3½ years and 11 months, respectively, were negative to both the above dilutions.

From the Kiev Medical Institute in Russia comes a report by Kaljus [7] of a group of 66 cases of trichinosis. Forty-nine showed positive skin reactions and in three of these the first positive response was observed 120, 252, and 380 days, respectively, after the onset of illness. Of five other patients, four gave positive reactions five months, eight months, thirteen months, and two years after infection; another was negative after four years. The same antigen was used but in 1 : 1000 dilution.

A different approach to this matter was used by Schapiro, Crosby and Sickler.[8] They applied a 1 : 10,000 dilution of the Bachman antigen to 400 unselected patients in a municipal hospital. Simultaneously a study of diaphragms of those who came to necropsy was carried on. By the routine skin tests they found 18.25 per cent positive reactions; by a study of the diaphragms at post mortem 19.1 per cent contained encysted trichinellae. There were 73 cases with positive skin reactions; 27 of these subsequently came to necropsy and only three of the diaphragms were negative. Three hundred and ten cases had negative skin reactions. Eighty-nine came to necropsy and encysted trichinellae were found in the diaphragms of only two. In their study the immunologic and pathologic observations were made by different investigators.

Theiler, Augustine and Spink [5] found in the literature observations on persistent eosinophilia as follows:

3 months after infection	8% eosinophiles (Staubli)
3 months after infection	7% eosinophiles (Staubli)
6 months after infection	34.7% eosinophiles (Brown)
6 months after infection	7.1% eosinophiles (Staubli)
1 year after infection	7% eosinophiles (Staubli)
3 years and seven months after infection	8% (two cases) (Weindrack)

In a group studied by them two cases, 7 and 5½ years after infection, still had 5 per cent eosinophiles.

In another of Brown's [9] cases 16.8 per cent eosinophiles were found 16 to 17 weeks after the onset of symptoms.

The epidemic of trichinosis in Portland during February and March of 1935 [10] provided an unusual opportunity to put the skin reaction to clinical test. Early in January of that year a prosperous Italian contractor purchased two pigs from a farmer in a nearby town. The pigs had been fed on garbage from an F.E.R.A. camp. In Portland they were fattened on corn and milk, slaughtered, and one of these pigs was sold on shares by the contractor to two of his employees. Most of the meat from this carcass was made into a favorite Italian sausage at home and dispensed widely among friends. The sausage was eaten raw or after very little cooking. All the cases of trichinosis in the epidemic occurred among those who had eaten the meat from this pig. Once the source of infection had been found, it was an easy matter to trace the dispersal of the meat, and in a sample of the pork obtained for microscopic examination encysted trichinellae were found. Seventy-one persons are known to have eaten of the infected meat, and positive skin reactions, eosinophilia, or both were observed in fifty-four. The study of the epidemic took place in February, March, and April, 1935. One or more eosinophile counts and skin tests were made on every person who had been exposed. A 1: 10,000 dilution of the Bachman antigen was used for the intradermal test. Three years later, in March, April, and May of 1938, we undertook to retest these persons in the same way. We were able to retest 45 of the 52 survivors. The results are recorded in the appended table.

In the original study we reported the cases as follows:

Died	2
Persons ill with definite trichinosis but recovered: Every one of these individuals had eosinophilia and a positive skin reaction during his illness	22
Persons who had no symptoms but who had both eosinophilia and a positive skin reaction	9
Persons who had eosinophilia but negative skin reaction: This group includes two who were ill after having eaten the infected meat, but whose symptoms were not characteristic of trichinosis. Both these patients were treated at home by other physicians	16
Persons who were not ill, had no eosinophilia, but did have a positive skin reaction	5
Total	54

Of the 22 persons who were ill with definite trichinosis but recovered, 20 submitted to the tests three years later. Seventeen of them still showed positive reactions, and three were negative; thus 85 per cent had remained positive after three years. There was observed, however, a tendency for the reaction to be less striking. In five cases the reaction was approximately as marked as at the first test. One woman only had a more marked reaction when retested, 2 + instead of 1 +. The other 14 reactions at the more recent testing were less marked, 3, 2, or 1 + or 0 instead of 4 +. This change is in agreement with the observations of Theiler, Augustine and Spink on testing, after four to nine years, persons who had been hospital patients with the disease. Their two oldest cases, 9 and 7½ years after recovery, did not react to the skin test, while their three more recent cases did react.

Eight of the group of nine who had exhibited eosinophilia and positive skin reaction without symptoms were retested. Six of the eight still reacted; two did not. In four instances the reaction was of approximately the same degree. In four it was diminished or absent: thus 75 per cent of this group maintained their ability to react after three years.

Twelve of the 16 who had reacted to their exposure by showing eosinophilia alone were retested. Only one had developed a positive skin reaction. This unexpected reversal of the skin reaction was found in one of the two persons who had been ill after eating infected meat, but whose illness might not have been trichinosis.

The five persons found to have positive skin tests without eosinophilia at the time of the epidemic were retested. Four had lost their positive skin reaction. In one it had increased from 3 + to 4 +.

These last two groups are rather unsatisfactory for statistical analysis. Improperly cooked pork is considered a delicacy by these people of whom we speak, and the positive skin reaction without eosinophilia at the original testing may quite possibly have been the last sign of some previous infection.

TABLE I

Comparative Skin Tests and Eosinophile Counts, 1935 and 1938

	Case	Age	1935			1938		
			Skin Test	Eosinophiles	Total W.B.C.	Skin Test	Eosinophiles	Total W.B.C.
Died	Mrs. A. F.	45		3 %	17,500			
	D. D.	40		24 %	12,000			
Persons ill with definite trichinosis, recovered	R. F.	44	4+	74 %*	15,000	4+	4 %	10,000
	D. F.	10	4+	19 %	12,800	2+	1 %	7,000
	A. F.	11	4+	51 %	9,400	3+	1.5%	5,800
	T. F.	23	4+	12.5%	12,000	1+	5 %	8,000
	J. F.	14	4+	50 %	15,400	3+	1 %	7,000
	R. F., Jr.	2	4+	70 %*	34,000	4+	4 %	8,000
	L. M.	32	4+	4 %	17,000	2+	2.5%	6,900
	A. P.	22	4+	58 %	15,600	4+	1.3%	9,500
	A. A.	55	4+	13 %	13,000	3+	.5%	11,600
	C. F.	36	4+	33 %	12,200	3+	7 %	11,400
	P. F.	10	4+	38 %	23,000	3+	2 %	11,700
	Mrs. D. D.	44	4+	30 %	14,000	3+	3 %	6,800
	A. D.	17	4+	5 %	10,000	2+	1.5%	14,200
	R. A.	45	4+	15 %	10,000	4+		11,000
	H. A.	23	4+	38 %	13,000	4+	1.3%	5,000
	O. R.	21	4+	56 %	24,300	2+	1 %	13,800
	L. F.	7	4+	32 %	7,800	2+	7.3%	10,000
	D. F.	13	4+	58 %	18,800	neg.	1.3%	9,800
	Mrs. C. F.	35	4+	58 %	13,200	neg.	3.5%	11,700
	O. B.	12	3+	33 %	19,600	neg.	5 %	6,000
	N. M.	14	4+	21 %	12,600			
	Mrs. R. A.	47	2+	8 %	11,000			

* Highest of several determinations.

† Ill during the epidemic, symptoms not characteristic of trichinosis, treated at home by other physicians.

TABLE I—*Continued*

	Case	Age	1935			1938		
			Skin Test	Eosinophiles	Total W.B.C.	Skin Test	Eosinophiles	Total W.B.C.
Persons without symptoms—eosinophilia and positive skin test present	Mrs. E. B.	48	2+	4.3%	12,500	1+	1 %	10,000
	L. B.	5	4+	39 %	15,100	3+	5 %	8,000
	T. A.	16	2+	6 %	17,600	2+	1 %	11,300
	F. A.	20	4+	6 %	9,800	4+		15,900
	M. A.	18	2+	9 %	13,200	2+	1 %	7,000
	A. D.	44	2+	7 %	13,300	neg.	4.5%	10,600
	T. D., Jr.	2	2+	5.5%	10,000			
	A. B.	11	4+	39.5%	15,700	neg.	2 %	7,100
	A. F.	8	2+	19 %	20,000	2+	3 %	8,900
Persons without symptoms—eosinophilia present, skin test negative	J. M.	12	neg.	2.3%	22,900	neg.	4 %	13,600
	L. M.	10	neg.	10 %	17,000	neg.	6 %	11,800
	J. M.	8	neg.	7 %	20,000	neg.		
	C. M.	6	neg.	5 %	24,200	neg.	10 %	17,500
	A. M.	38	neg.	7 %	13,100	neg.	1.5%	
	E. B.†	33	neg.	28 %	14,000	3+	3 %	9,900
	J. B.	35	neg.	12 %	14,000			
	C. B.	10	neg.	21 %	13,000	neg.	1.5%	9,000
	M. B.	8	neg.	33 %	16,400	neg.	4 %	10,500
	J. R.†	7	neg.	23 %	14,000	neg.	3 %	12,200
	E. B.	48	neg.	4.3%	12,500	neg.	3 %	12,000
	N. D.	10	neg.	11 %	19,000	neg.	3.5%*	32,000
	A. D.	36	neg.	5 %	13,000	neg.	3 %	10,400
	S. D.	7	neg.	5 %	16,000			
	A. F.	12	neg.	7.5%	11,000			
	J. D.	4	neg.	10 %	13,000			
Persons without symptoms—eosinophilia absent, skin test positive	F. B.	13	3+	2 %	9,200	neg.	.5%	7,500
	F. O.	55	4+	3 %	8,000	4+	2 %	6,000
	M. N.	33	3+	2 %	6,000	neg.	2 %	7,800
	A. D.	33	4+	3 %	8,000	neg.	3.5%	9,400
	A. B.	21	3+	3 %	6,000	neg.	2.5%	7,000

Persistent eosinophilia of over 500 per cu. mm. was observed in six individuals in this present study. The total white counts and eosinophile percentages were as follows:

C. F. 7% of 11,411 = 798
L. F. 7.3% of 10,000 = 730
J. M. 4% of 13,600 = 544
L. M. 6% of 11,800 = 708
C. M. 10% of 17,500 = 1750
N. DiB. 3.5% of 32,000 = 1120
whose count one day later was
3.5% of 18,800 = 658

All these white counts are high normal or above normal so we do not care to draw any conclusions from them. They suggest that while eosinophilia is rarely present three years after infection with trichinellae, the leukocytic response to other ills may contain more than the usual number

of eosinophiles. It has, however, been shown that intercurrent infection in acute trichinosis causes the disappearance of eosinophiles in the blood smear.[11]

SUMMARY

1. In persons who have been ill with clinical trichinosis the Bachman intradermal skin reaction remains positive after three years in the great majority of cases, although there is a tendency toward a less marked reaction.

2. In subclinical trichinosis with a negative skin reaction the skin test is also negative after three years.

3. Eosinophilia is usually absent three years after recovery from trichinosis.

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THE USE OF HISTAMINE IN RHEUMATOID ARTHRITIS *

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There can be little doubt that arthritis and allied conditions are assuming a deservedly more important place in the thoughts of both the clinician and the research worker. In spite of much recent work, however, a satisfactory basis for treatment has not been established, and some treatments are expensive and complicated. Fever therapy, hydrotherapy, etc., seem to give great relief but are difficult of attainment under ordinary circumstances. The production of artificial jaundice advocated by Hench is difficult to obtain because of its dangers and expense.[1, 2, 3, 4]

It is true that certain forms of physical therapy can be administered in the home using improvised equipment, and all such measures should be employed since the more comprehensive and inclusive the treatment the more satisfactory will be the results.

Certain drugs having a vasomotor effect have been administered with some success by means of iontophoresis. This procedure requires a suitable apparatus for administration and to this extent is handicapped. Some drugs which are administered by iontophoresis will produce their effects when given by mouth or subcutaneously but the effects produced by such administration are not always as satisfactory as when the drugs are given by iontophoresis. Histamine diphosphate seems to be an exception. Histamine has been administered to arthritics in a variety of ways, with varying results. Medical iontophoresis is the method advocated for administration by most investigators. It has been given, however, by mouth, by injection, and as an ointment.

Our experience with the drug includes administration by ointment, subcutaneous injection, and iontophoresis. We have administered the drug by iontophoresis and succeeded in getting general reactions such as fall in blood pressure, flushing, palpitation. This method was time-consuming and difficult to continue after the patient left the hospital. We have used histamine ointment alone, mixed with a rubefacient such as capsicum, and also combined with various forms of salicylates. None of these ointments produced either general or local response of sufficient degree to be helpful, and our recent experiences with commercial preparations of histamine ointment have been no better. We then resorted to subcutaneous injections of histamine with the results reported in this communication.

Deutsch [5] was perhaps the first to report on use of histamine by iontophoresis. He had used other methods of administration but finally concluded the iontophoresis was the most satisfactory. Deutsch first used his-

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From the Arthritis Division, St. Louis University Group of Hospitals.

tamine in an attempt to simulate fever therapy, since he felt that the reactions associated with fever therapy arose from histamine-like reactions in the tissues. He pointed out that histamine was particularly efficacious in soft tissue involvements such as bursitis and fibrositis, and in this opinion we must concur. The polyarthritic according to Deutsch was benefited but never cured by the administration of histamine, and this has been our experience.

Kling[6, 7] in this country reported, rather enthusiastically, on the use of histamine in the treatment of arthritis. He experimented with various methods of administration and, at one time, scarified lightly the tissue about the involved joints and applied the histamine. In this way reactions could be obtained, but they were erratic and the scarifications took considerable time to heal, so that eventually the method was abandoned for iontophoresis. Kling and Sashin[8] brought out the fact that a combination of drugs given by iontophoresis may react better than one drug alone. Salicylates and histamine both given by iontophoresis seem to be such a combination. They also emphasized the advantages of histamine over other forms of physical therapy in soft tissue disease, finding that bursitis, tenosynovitis, and fibrositis responded well.

Shanson, Barnett and Eastwood,[9] working in England, reported favorably on the injection of histamine subcutaneously in arthritis. They used histamine diphosphate and thio-histamine and concluded that the diphosphate was the drug of choice.

Procedure

In an attempt to evaluate the importance, if any, of subcutaneously administered histamine to the patient suffering from rheumatoid arthritis, the following study was carried out.

Ten patients suffering from rheumatoid arthritis were selected; the criteria being that only patients who had been followed by us for one year or more and who seemed likely to coöperate were to be used. No change in their therapy was made. Physical therapy, salicylates, exercise and occupational therapy were continued. In addition to these things, however, histamine injections were started. The frequency of injections varied with conditions but were essentially the same for a particular patient. Hospitalized patients were injected twice a day, ambulatory patients returning to the Outpatient Clinic were injected three times a week and other patients, who consented, were injected at home once daily by someone of the family trained in the use of the syringe. The diphosphate was the salt used and was supplied through the courtesy of Eli Lilly and Company. It was made up in Coca solution, in dilution of 1–1000. It was kept in dark bottles in refrigerator until used. The solution seems fairly stable and can be kept in a cool place outside the refrigerator, if necessary.

It was soon noted that the individual tolerancy to histamine varied and a test dose of 0.1 c.c. was given to each patient, this dose being increased by 0.1 c.c. until the reaction level was reached. This reaction-producing

dose was then maintained until the patient's tolerance increased. Increased tolerance was determined by failure to react to the usual dose. In our experience 0.4 to 0.6 c.c. is the range of effective dosage, and it is our experience that tolerance is only rarely increased, since patients who react to a given amount will continue to react at that level for three to six months.

The patients were told to report any change in symptoms and were also asked about their sensations immediately after injections. We attempted, so far as possible, to avoid suggesting symptoms which might be expected from the drug and we did not tell the patients in what way we thought they might benefit. Patients were urged to continue injections for one month and were then told that they might continue or not. It was felt that the patient would in that way evaluate the results of the treatment more accurately.

Only individuals suffering from rheumatoid arthritis are considered in this study.

Results

The immediate reaction to injection of histamine varies, naturally, with the size of the dose and the susceptibility of the patient. Patients vary considerably in their response to the drug, but each individual responds in essentially the same manner to subsequent injections. In none of the cases were the reactions severe enough to incapacitate the patient.

The chief symptoms noted are headaches, flushing, palpitation, sweating, nausea, dizziness and weakness. The headaches are rather constant, come quickly after injections, and are dull and throbbing; they are felt chiefly on the top of the head. The headache leaves in about 10 to 15 minutes unless too large a dose of the drug has been given. Flushing is also a common symptom. The patient notices a feeling of warmth, and the skin becomes red and warm to the touch. This lasts for 5 to 10 minutes and may be followed by a moderately profuse sweat. The flushing seems essential to the success of the treatment, since those patients who did not flush failed to get relief from pain and stiffness.

Palpitation was not a constant finding and was never alarming. Tachycardia was noted in all cases at the height of the reaction and it was at this point that nausea and faintness were occasionally complained of. It was at this point, too, that the blood pressure found its lowest level. The entire reaction rarely lasted 15 minutes and was never alarming. Following the reaction, relief from pain and stiffness was noted by most patients. There seem to be few contraindications to the use of histamine in the amounts used by us. Senility, marked vasomotor instability, marked arteriosclerosis, cardiac decompensation and hypotension would seem to represent conditions in which the drug should be administered with great caution or not at all. Table 1 gives a brief resumé of duration, sex, principal joint involvement, etc. in this group of cases.

TABLE I

Number	Sex	Age	Type	Duration	Primary Symptoms
6986	M	30	Rheumatoid arthritis	7 yrs.	Deformity, fixation and stiffness.
2040	F	54	Rheumatoid arthritis	3 yrs.	Swelling of joint. Weakness. Mild deformity.
4270	M	22	Rheumatoid arthritis	4 yrs.	Marked deformity. Limitation of motion and stiffness.
1042	F	29	Rheumatoid arthritis	2 yrs.	Slight deformity. No fixation. Pain.
5706	F	42	Rheumatoid arthritis	5 yrs.	Marked deformity. Fixation and stiffness.
1070	M	27	Rheumatoid arthritis	4 yrs.	Fixation of back, hips and knees. Marked stiffness.
H22518	F	43	Rheumatoid arthritis	11 yrs.	Deformity and fixation of joints of lower extremities.
39682	F		Rheumatoid arthritis		Deformity and fixation of lower extremities. Upper less markedly involved.
36–9198	M	35	Rheumatoid arthritis	6 yrs.	Fixation of neck, hips and knees.
34–9228	F	42	Rheumatoid arthritis	4 yrs.	Fixation of knees and involvement of upper extremities.

Table 2 is an attempt to present the results in a compact form. It will be noted that of 10 cases, seven were definitely benefited, inasmuch as increased motion and, in most instances, relief from pain were noticed. All of these patients felt that their extremities were warmer than usual and there was a sense of well-being which they had not noticed for some time. This sense of improved well-being manifested itself in numerous ways. Increased activity, improved appetite, greater cheerfulness were some of the subjective changes noted. Physical therapy was less tedious since it was less difficult for the patient to be moved about.

One of the seven patients, who admitted relief from stiffness, objected to the injections to such an extent that they were discontinued after two and one-half months.

There are three failures, and a brief analysis of these is of interest. Case 6986 was a young man 30 years of age who had had arthritis for seven years. He had a complete ankylosis of the spine and the hips were fixed. He had had manipulation under anesthesia at another institution, and roentgen-ray examination of hips when he entered the Firmin Desloge Hospital revealed bilateral fracture of the necks of the femurs. The head of the right femur was practically absorbed. He had a positive gonococcal fixation test, pus in the prostate, and fissure in ano. It is felt that, in spite of the

TABLE II

Number	No. Injected	Dose	Duration	Reaction	Results
6986	65	2–6 minims	2 mos.	Flushing Sweating Nausea (mild)	Noted slight improvement in motion but this did not persist.
2040	36	4–8 minims	3 mos.	Dizziness Headache Sweating	Marked increase in motion. Diminished pain. Improvement has persisted without treatment for 3 months.
4270	32	6 minims	3 mos.	Headache Flushing Sweating	Marked improvement in motion which has persisted for 9 months.
1042	19	6 minims	19 days	Flushing Palpitation Sweating	No beneficial results and refused more injections.
3706	130	10 minims	3 mos.	Flushing Headache Palpitation Sweating	Noted increased motion during injections and requested continuation — no permanent results.
1070	280	10 minims	5 mos.	Flushing Nausea (mild) Headache Sweating	Felt much better during treatment. Stiffness improved to point where patient was up and about. Improvement persisting.
H22518	725	10 minims	2 yrs.	Flushing Headache Palpitation	Was able to move about after injections — effect noted for from 4 to 6 hours.
39682	60	6 minims	2 mos.	Headache Palpitation	Patient felt only slightly helped and injections were discontinued.
369198	105	6–8 minims	3 mos.	Nausea Palpitation Sweating	Noted increased motion after injections and diminution in pain.
34-9228	85	8 minims	2½ mos.	Palpitation Flushing Abdominal discomfort	Patient objected to the injection and although motion was improved treatment was discontinued.

distribution of the arthritis and the roentgenograms which were more or less characteristic of rheumatoid arthritis, this patient was suffering from polyarthritis of gonorrheal origin. This form of arthritis is not rare and taxes the ingenuity of the best diagnostician. In fact, it is impossible in the late stages to differentiate it satisfactorily from rheumatoid arthritis. In any event the patient showed only a slight and temporary improvement on histamine to which he was, incidentally, quite sensitive and, after two months, injections were discontinued.

The second failure, case 1042, was a female, 29 years of age, with early rheumatoid arthritis. She had 19 injections of the drug, got satisfactory

reactions, but did not feel that they helped her and, after 19 days, refused more injections.

The third case, 39682, was also a female with quite marked involvement of the legs. The knees were fixed in flexion, and there was limitation of motion of the hips. This patient took daily injections for two months, had definite increase of motion in the hip joints, and was able to walk with the aid of a cane. The staff considered her a case which had been aided by injections, but she felt that she was very little benefited. She asked that injections be discontinued; this was done and she was classed as a failure.

Of the other cases treated, most drifted away from the treatment after periods of from three to five months. One case stands out because of the duration of the treatment.

Case 22518, a very intelligent, coöperative school teacher, when first seen in the clinic was unable to work and without funds. She improved on physical therapy, massage, etc., but continued to be extremely stiff on awakening in the mornings. Her "limbering up" period lasted 30 to 45 minutes, and, because of the stiffness, physical therapy and other activities were very difficult. She was placed on histamine and noted immediate and marked relief from stiffness. She eventually returned to teaching and for two years has given herself an injection of histamine before arising in the morning. The drug decreases stiffness and pain in this individual to such an extent that without it she can do much less than when she takes the injections regularly.

Summary

Histamine diphosphate dilution (1–1000), when properly given to individuals without complete ankylosis of the joints, will increase motility and frequently relieve pain. The subcutaneous administration of the drug seems to be as satisfactory as iontophoresis and is far superior to the use of the ointment in our hands.

Histamine will not cure arthritis. It is at best an adjunct to other forms of therapy and, as such, may be expected to aid in some cases and to fail in others. When such failures are encountered, the drug should be immediately discontinued.

The drug should be administered cautiously to avoid severe reactions. In our experience no shock has been encountered which necessitated treatment. There seems to be no cumulative or deleterious effect from the drug. There was no alteration in blood chemistry, blood pressure, red blood cell count, etc., from the levels determined at the onset of therapy.

Since patients do not readily develop a tolerance for the drug, it can be administered over long periods of time.

Histamine, although not having a specific therapeutic effect in rheumatoid arthritis, when given subcutaneously does seem to be of value in the symptomatic treatment of the disease. It apparently enhances the value of other forms of therapy and, in many instances, enables the patient to carry on activities which would otherwise be impossible.

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SUBACUTE BACTERIAL ENDOCARDITIS IN OLDER PEOPLE*

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THE occurrence of a specific disease may vary, not only in the incidence with which it afflicts a number of individuals, but also in the relative number of individuals differing by age, sex, or other factors. How much middle life or late maturity may alter the reaction of the individual to the same disease is a question not entirely clear. It is becoming a more important one in view of the aging of the population and the greater number of older people incurring acute infectious as well as chronic degenerative diseases. In disease of the cardiovascular system, this age variation is most pronounced.

Types of disease that involve the young heart may be entirely different from those afflicting the older heart. Arteriosclerotic disease of the heart seldom develops in young individuals. Acute rheumatic carditis or endocarditis is almost never found in the very old. Differences in the reaction of normal young and normal old hearts to similar physiological conditions have only recently been investigated. Differences in the effect on the young and the senescent heart, of unusual physiological conditions or of disease have been seldom defined. If differences are present, they may be, as Cohn [1] has remarked, striking; for instance, compensation for cardiac defect by hypertrophy is a form of repair incomplete or deficient in old age.

One method for analyzing such differences is the consideration of the effects of a disease that attacks both old and young hearts. Subacute bacterial endocarditis, because of its association with rheumatic heart disease, has been considered an affliction chiefly of younger individuals. Though it will probably remain an illness largely of adolescents and young adults, its more frequent occurrence in older subjects may be expected. Arteriosclerosis, hypertension, and syphilis may, like rheumatic fever, damage the valvular tissue and provide a suitable basis for vegetative endocarditis. If the lives of patients with rheumatic heart disease should be prolonged by increasingly efficient care, the complication of subacute bacterial endocarditis may be postponed to their later years.

This study concerns the appearance of subacute bacterial endocarditis in a number of patients over 40 years of age. The information obtained has been clinical and anatomical.

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Method

Clinical and pathological information has been obtained on 28 patients over 40 years of age, observed on the Third (New York University) Medical Division of Bellevue Hospital, from October 1931, to January 1938. Only those cases with diagnosis established by necropsy have been considered; some were under personal observation, the records of others were analyzed. The oldest subjects were 70 and 72 years of age, of whom there were two, both women. Of the 28, 23 were men. In 14 cases the correct antemortem diagnosis was made. During the same period, according to the clinical observations, 25 patients, under 40 and over 12 years of age,* succumbed to subacute bacterial endocarditis. On 12, necropsy was permitted and the premortem diagnosis confirmed. From the records of this service it appears that subacute bacterial endocarditis has been correctly diagnosed in those under 40, and not sufficiently considered in those over 40 (figure 1). In addition it should be pointed out that of the group

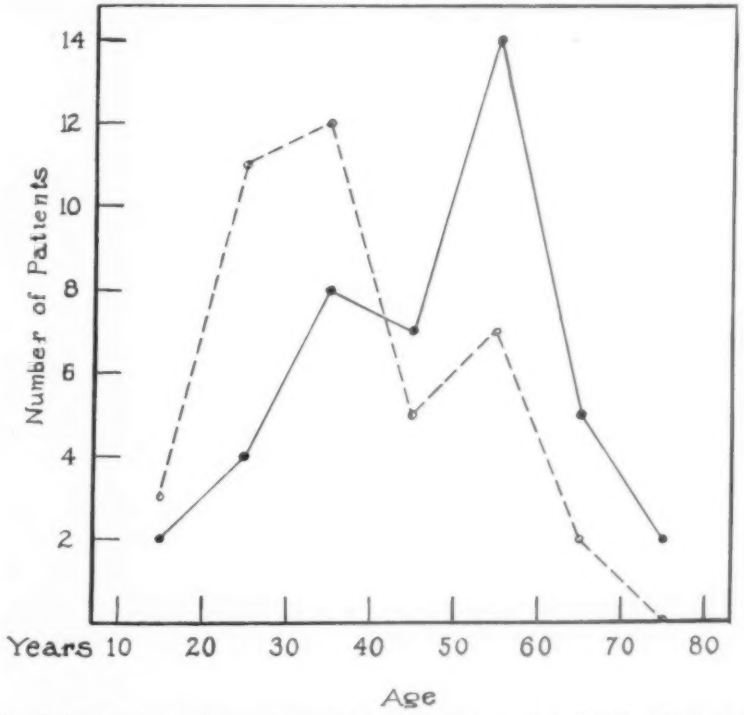

Fig. 1. Subacute bacterial endocarditis. Patients on the Third Medical Division, Bellevue Hospital, October 1931 to January 1938. These curves show the distribution in different decades of life, according to the clinical diagnosis (broken line - - - -), and according to the anatomical diagnosis (uninterrupted line ——). See text for comment.

over 40 the average age of the correctly diagnosed was 51 years, and of the undiagnosed, 59 years.

* Patients under twelve are not admitted to this service. According to other experience, subacute bacterial endocarditis seldom afflicts individuals before the second decade.[5, 8]

Clinical Observations

As has been remarked, of the 28 patients, 14 cases or one-half were correctly diagnosed clinically, as examples of subacute bacterial endocarditis; the other 14 were not. It is fair to state, however, that in the incorrectly diagnosed group, subacute bacterial endocarditis was often suggested in the differential diagnosis, but the clinical signs and symptoms and the laboratory findings did not confirm this unequivocally as the final clinical diagnosis, and hence it was not made. With two major exceptions, the symptoms and the physical findings were similar in the two groups; all but two had signs of heart disease, all but two had signs of infection. In the group with correct diagnoses cultures of the blood were positive, or embolic phenomena such as petechiae, so indicative of endocarditis in the course of heart disease, were present. In the group without correct diagnoses, complications in other organs, secondary to the endocarditis, were interpreted as the primary disease. In the 14 cases in which the clinical diagnosis of subacute bacterial endocarditis was not made, the final diagnosis at the bedside was: in four, rheumatic heart disease; in four, malignant disease of the kidney; in two, chronic diffuse glomerular nephritis; in one each, luetic and hypertensive heart disease, luetic heart disease, hypertensive and arteriosclerotic heart disease, and streptococcus bacteremia of unknown origin.

One may observe from this tabulation that the differential diagnosis involves primarily either rheumatic heart disease, because of cardiac involvement and infection, or renal disease, because of hematuria. If the events of an incorrectly diagnosed illness are viewed in retrospect, one will find the usual known features of subacute bacterial endocarditis, as follows:

Case 1. A 69-year-old male complained of dyspnea, fatigue and epigastric distress on admission to the hospital. Three months previously he had suffered a cold and an attack of severe precordial pain. In the three following weeks, edema of the ankles and dyspnea were present. Thereafter the cardiac reserve gradually declined.

The patient was undernourished, pale and elderly in appearance. The rectal temperature was 100.8° F. The heart appeared enlarged; a systolic murmur was heard at the base and at the apex. The pulse rate was 90 per minute; the systolic blood pressure was 154 mm. Hg, the diastolic 70. Râles were heard at the bases of the lungs, and there was edema of the ankles. The count of the red blood cells was 3.36 million per cu. mm.; that of the white cells 6,300. A few red cells were present in the urine. During the remaining 90 days of life, the temperature varied from normal to 103°. The hematuria was variable, apparent sometimes on gross, at other times on microscopic examination. The count of the red cells in the blood fell to 1.7 million; by transfusion and diet it was increased to 2.2 million. The chemical constituents of the blood were normal. Blood pressure was usually 124 systolic, 48 diastolic. Digitalization had no effect on the congestive heart failure. A yellowish tint developed in the skin; the icteric index was normal. Repeated cultures of the blood were negative. The patient gradually failed, becoming comatose before death. At necropsy, the principal findings were lobular pneumonia, and subacute bacterial vegetative endocarditis of the aortic and mitral valves (figure 2). The leaflets of these valves showed moderate sclerotic thickening of the borders. The heart weighed 420 grams. The spleen was enlarged, weighing 390 grams. The kidneys were normal except for some tubular hemorrhage. There was acute, focal suppurative prostatitis.

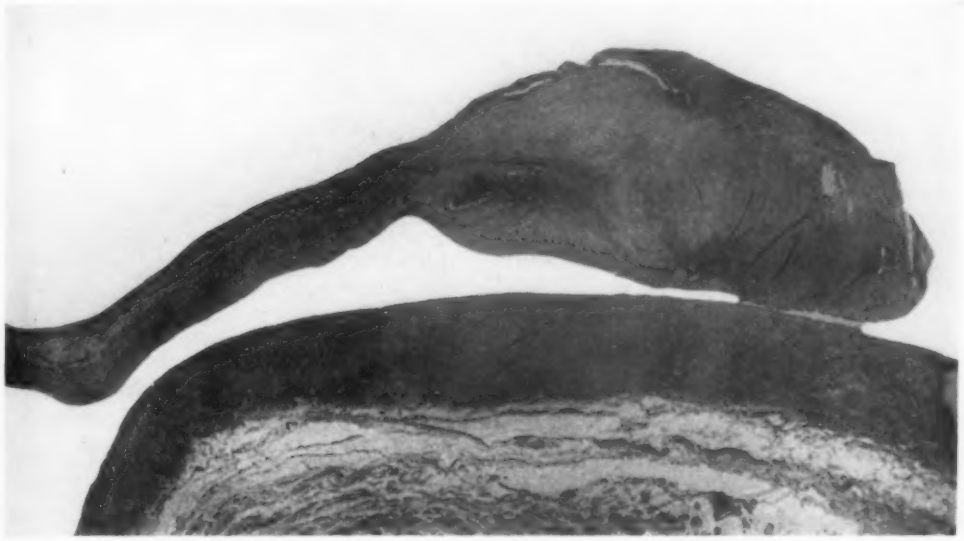

FIG. 2. Subacute bacterial endocarditis and arteriosclerotic heart disease. Section from a leaflet of the mitral valve of a man, aged 69 years (Case 1). The distal portion of the leaflet is thickened and had undergone sclerotic changes with fibrosis and deposition of cholesterol crystals. On the upper border is a vegetation composed of fibrino-purulent exudate, partly organized and containing bacteria. No anatomical evidence of rheumatic infection was found.

The features presented by the illness in this patient are similar to those in Case 2, in which the diagnosis was rendered obvious by the positive blood culture.

Case 2. A 50-year-old Italian waiter was admitted with the complaints of progressive weakness of three and a half months' duration, of increasing edema of the feet of seven weeks' duration, and of "red spots" in the skin of five weeks' duration. Three attacks of epistaxis occurred in the preceding ten days. There was no knowledge of hypertension or of lues, or of manifestations of the rheumatic state.

He was dyspneic and orthopneic. Petechial hemorrhages were present in the conjunctival sacs. The heart, with a diffuse and heaving apical impulse, was enlarged; there were a harsh, blowing apical systolic murmur, and a blowing basal systolic murmur; the rhythm was regular. The systolic blood pressure was 100 mm. Hg, diastolic 68. The liver edge was felt two fingers' breadth below the right costal border, and the spleen was just palpable. There were old and recent purpuric hemorrhages over the legs and thighs.

The urinalysis revealed consistently a few red blood cells. The count of the red blood cells ranged from 2.0 to 2.5 million per cu. mm.; that of the white cells from 8,000 to 11,000. The chemical constituents of the blood were normal; the Wassermann reaction was positive. The sedimentation rate of the erythrocytes was normal. The electrocardiographic studies revealed left deviation of the electrical axis with A–V nodal tachycardia, and the teleroentgenogram showed enlargement of the heart. Three blood cultures were positive for *Streptococcus viridans*.

While on the ward, the patient's temperature varied between 101° and 103°. Numerous petechiae appeared from day to day. Digitalization did not affect the congestive heart failure, and the patient became more cachectic and died after 22 days in the hospital, five months after the onset of symptoms.

The necropsy revealed subacute vegetative endocarditis of the tricuspid, mitral and aortic valves. From the vegetations *Streptococcus viridans* organisms were cultured. Sclerosis of the valves, due to degenerative (non-infectious) changes was confirmed by microscopic study. There were infarcts in the kidneys and spleen, and histologic study confirmed the diagnosis of focal embolic glomerulo-nephritis. There was generalized anasarca of the serous sacs and lower extremities.

Correlation of Clinical and Pathological Findings

Clinical findings and their verification by necropsy * may be considered on the basis of general symptoms of infection, involvement of the heart, hematological effects, and peripheral effects.

A. Symptoms of Infection: The major complaints were usually lassitude, weakness, feverish and chilly sensations, and headache—symptoms commonly associated with febrile illness. Signs of infection were manifested in 26 of 28 patients; the appearance was febrile, the temperature was elevated, the skin was cold and clammy, or warm and moist, and the face was flushed or pale. In 12, signs of infection in the heart were manifested by tachycardia, changing murmurs, and by exclusion of involvement in other organs. In five, the signs and symptoms of systemic infection could not be localized.

Comment from necropsy: Infectious endocarditis was present in all of the 28 cases.

B. Involvement of Heart: Clinical indications of heart disease were present in all but one of the patients. The antemortem diagnosis of rheumatic heart disease was made in 10, of arteriosclerotic heart disease in two, of luetic heart disease in four, and, in one each, of luetic and hypertensive heart disease, arteriosclerotic and hypertensive heart disease, and arteriosclerotic and luetic heart disease. In nine the underlying heart disease was unknown in type or not recognized. Congenital bicuspid aortic valve was not mentioned.

Comment from necropsy: The cardiac lesions were the result of:

Anatomical Heart Disease	Number	Age	
		Average	Range
Rheumatic	16 (57%)	53 yrs.	42 to 70 yrs.
Arteriosclerotic	7 (25%)	62 yrs.	50 to 72 yrs.
Luetic	2 (7%)	52 yrs.	47 and 58 yrs.
Congenital bicuspid aortic valve	3 (11%)	55 yrs.	48 to 69 yrs.

1. A murmur or murmurs were found in all patients. A systolic murmur was noted at the apex in 27; it was noted at the base in 19, and always in conjunction with a systolic murmur at the apex. A diastolic murmur was

* Dr. Eugene Clark, Assistant Pathologist, Bellevue Hospital, kindly advised us in the review of the pathological material.

noted at the apex in 11, and at the base in 15, of whom eight also presented the apical finding. A thrill was observed less frequently; it was felt during systole in six and during diastole in four.

Comment from necropsy: Endocardial vegetations were present as follows:

in 9 on the aortic and mitral valves;
in 8 on the mitral valve only;
in 7 on the aortic valve only;
in 2 on the aortic and tricuspid valves;
in 2 on the aortic, mitral and tricuspid valves.

All but one of the vegetations occurred on valves deformed by one of the aforementioned predisposing conditions; in the exception the vegetation developed on the mitral valve in a heart with congenital bicuspid aortic deformity.

2. Enlargement of the heart was noted clinically in 27 patients.

Comment from necropsy: In 24, the weight of the heart indicated hypertrophy. The mean weight was 571 grams; the greatest weight 1,080 grams in a male patient with longstanding syphilitic heart disease.

3. Electrocardiograms were obtained on 24 patients. In 20 the rhythm was normal, but eight of these had tachycardia. In one, aged 42, with known rheumatic heart disease for 32 years and marked rheumatic mitral deformity, auricular fibrillation had been present throughout the observation in the hospital and for nine months previously; although three blood cultures showed no growth, the diagnosis of subacute bacterial endocarditis was correctly made on the basis of splenomegaly, typical petechiae in the skin and conjunctival sacs, and the febrile course. Another case of advanced rheumatic mitral disease with established auricular fibrillation and subacute bacterial endocarditis has been reported from this clinic.[2] In another, aged 62, with hypertensive and arteriosclerotic heart disease, auricular fibrillation developed during the last few days of life. In two, nodal rhythm was present.

4. Congestive failure developed in 25—being present in 15 for more than four weeks, and in 10 shortly before death. The longest duration of failure was seven months. The average length of congestive heart failure was three and one-half weeks in the group of correctly diagnosed cases, and nearly twice that, or six weeks, in the 14 cases which did not receive a correct clinical diagnosis. Of 15 who received digitalis in adequate therapeutic amounts, therapeutic response did not occur in 12, and occurred only moderately in three.

C. Hematological Effects:

1. The blood count revealed an anemia in all patients, ranging from 1.9 million to 4.7 million red cells. The average red blood count was 3 to 3.4 million. The leukocyte count varied from 5,400 to 38,000; the average was 13,000 to 14,000.

2. Blood cultures were taken on 23 patients. Twelve, or a little over one-half, were positive; in eight the culture gave *Streptococcus viridans*, in two *Streptococcus hemolyticus*, and in two pneumococcus (Types 3 and 7).

Comment from necropsy: Postmortem cultures of the valve leaflets were positive in the 12 cases with positive cultures of the blood during life; in addition, *Streptococcus viridans* was cultured from the valves of two, and *Streptococcus hemolyticus* from the valves of six. Twenty (71 per cent) had bacteriological evidence of subacute bacterial endocarditis. No postmortem cultures were taken on the remainder.

D. Peripheral Effects:

1. Petechiae, either in the skin or the mucous membrane, were observed in 15 patients, but only in four of those in the incorrectly diagnosed group. Of the cases in which clubbing was found, six in all, all were diagnosed correctly. Of the 17 cases in which it was reported as missing, 11 were diagnosed incorrectly. In the remaining five, clubbing was not mentioned. The café-au-lait tint of the skin was recognized in six of the twenty-eight.

2. Enlargement of the spleen was recognized in 12 patients, four of whom were among the undiagnosed cases.

Comment from necropsy: The spleen was enlarged on postmortem examination in 26 patients; the weight varied from 230 to 1900 grams. There was infarction of the spleen in seventeen.

3. The kidney lesions were manifested clinically by hematuria in 17 or 60.7 per cent, and by renal insufficiency as measured by an increased nonprotein nitrogen content of the blood; 11 had definite azotemia, four were borderline in amount of nitrogen retention, ten were within the normal limits, and three were not examined in this chemical fashion. Using either renal insufficiency or hematuria as an index, we find 21, or 75 per cent, with clinical evidence of renal damage. One or both of these signs were present in 10 of the correctly diagnosed and in 11 of the incorrectly diagnosed group.

Comment from necropsy: The nephritides as presented by these older patients were often of a dual character. The total lesions are shown:

Pathological Diagnosis	No.	Per cent	
Focal embolic glomerulonephritis (alone or combined)	12	42.8	
Subacute diffuse glomerulonephritis (with focal lesions)	1	3.5	11 or 39.2 per cent
Acute diffuse glomerulonephritis (2 with focal lesions)	7	25.0	11 or 39.2 per cent
Chronic diffuse glomerulonephritis (2 with focal lesions)	3	10.5	11 or 39.2 per cent
Normal kidney	10	35.7	

Of the 12 cases with focal embolic glomerulonephritis, seven had positive blood cultures and six of these were correctly diagnosed as subacute bacterial endocarditis, while five had negative blood cultures and of these three were correctly diagnosed. Acute, subacute and chronic diffuse glomerulonephritis were divided among six cases with negative blood cultures, two with positive blood cultures, and three in which none were taken. Of this group of eleven, eight were correctly diagnosed as having subacute bacterial endocarditis.

Discussion

Frequent reports have described the clinical, bacteriological and anatomical features of subacute bacterial endocarditis.[3-19] Although Blumer[5] in 1923 considered that the "figures indicate that the disease is a disease of adolescence and young adults" (80 per cent of 317 patients were under 40 years of age), further observations (14) with present and future populations suggest a large and perhaps major incidence after the age of forty.

In the older patients considered here, the absence of positive blood cultures is an experience found, though less frequently, in younger patients. Bacteremia was not demonstrable in 11 (47 per cent) of 23 patients on whom cultures of the blood were taken; this is a higher percentage than observed in a younger group.[17] Embolic phenomena in the central nervous system, occurring in four, were less frequent than in reports regarding younger patients.[8, 11, 19] The frequency (64 per cent) of renal lesions, either focal embolic or diffuse inflammatory, is in accordance with, or less frequent than in other observations considering all ages.[10, 12]

Valvular deformity of rheumatic type occurred in 16 (57 per cent) of these patients, which is similar to the experience in younger groups.[7, 9, 14, 18] Sclerotic deformity of the valves was present in seven (25 per cent). Congenital bicuspid abnormality of the aortic valve was present in three (11 per cent), maintaining the observation[6] that it is a frequent association of subacute bacterial endocarditis. Lewis and Grant[6] observed that "amongst males, reaching adult life, and possessing congenitally bicuspid aortic valves, 23 per cent at least die of active endocarditis." Presumably a certain percentage die before forty.

Disturbances of cardiac rhythm were not frequent in these older patients —no more frequent than in other observations in a group with an average age of thirty-five.[16] Congestive heart failure, however, occurred more often; of the 28, it was present in 15 (53 per cent) for four weeks or longer, in 10 for one week to ten days prior to death; as pointed out above, the undiagnosed cases presented more difficulty in diagnosis because of longer periods of failure. In a predominantly younger group of 103 patients[13] circulatory function was considered excellent in 76, good in 17, and fair in 10; there were no data on eight additional cases.

Summary

The clinical picture of subacute bacterial endocarditis in individuals over 40 years of age is not as clearly defined as in younger individuals. Of 28 such patients considered in this report, only 14 received correct diagnosis before death. All cases of subacute bacterial endocarditis under the age of 40 which came to necropsy from the same Medical Service had correct clinical diagnoses.

One wonders, therefore, if the clinical picture of subacute bacterial endocarditis is different in older people. The features are essentially the same,

but they are less accentuated. The common or typical events of subacute bacterial endocarditis as seen in younger patients are not obvious in the older group because heart failure and azotemia are more often present. The latter findings are no doubt associated with decreased cardiac and renal reserve because of age. Subacute bacterial endocarditis is not often considered diagnostically in an elderly patient, who may or may not have congestive failure and who does not present signs, symptoms or history of rheumatic heart disease. A large proportion of the patients in this study (12 of 28) had arteriosclerotic or luetic heart disease, or congenital bicuspid aortic valves which formed an underlying basis for endocarditis. The blood culture was not so frequently positive, possibly because of increased immunity or less virulence of the infecting organism.

Otherwise the clinical events, as has been remarked, are essentially the same as in younger patients. All but two of this group had general signs of a febrile illness, and these two were among the undiagnosed cases. In addition, three of this latter group had a temperature course ranging below 100° F. They had signs of heart disease, perhaps with, perhaps without previous cardiac symptoms, but manifested by enlargement of the heart, by cardiac murmurs, changing or constant in character, and often associated with heart failure, progressive but often mild. Also, complications of moderate secondary anemia, moderate leukocytosis, frequently hematuria and azotemia, enlargement of the spleen, and peripheral embolic phenomena were consistently present.

Conclusions

1. Clinical and pathological observations on 28 individuals aged 40 to 72 years, who succumbed to subacute bacterial endocarditis, have been reviewed.

2. Subacute bacterial endocarditis in older people is associated with preexisting or chronic heart disease. The most common (57 per cent) is rheumatic heart disease, but other types of heart disease are also frequent.

3. The clinical features are essentially the same as those in younger patients, but less accentuated. Congestive heart failure and azotemia are more common; demonstrable bacteremia is less common.

4. Subacute bacterial endocarditis occurs more frequently than suspected or heretofore reported in older individuals.

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CASE REPORTS

CASE REPORT OF URINARY OBSTRUCTION DUE TO CRYSTALLINE CONCRETIONS FOLLOWING SULFAPYRIDINE THERAPY IN PNEUMONIA*

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This case report is presented in confirmation of the observation that urinary obstruction may occur during the course of sulfapyridine therapy as a result of the formation of sulfapyridine concretions in the urinary tract. A similar case, which yielded promptly to treatment, has recently been reported by Carroll, Shea and Pike.[1]

Many reports of gross hematuria following the administration of this drug have appeared in the literature. The occurrence of blood in the urine, under these circumstances, was at first ascribed to a "toxic nephritis." Evidence against this is the character of the abnormal urinary findings and the fact that the anuria disappears when the drug is discontinued. The possible significance of the deposition of actual crystalline concretions which result in the gross hematuria and anuria was first suggested by the animal experiments of Gross and his associates,[2] and Antopol and Robinson.[3] Almost simultaneously Southworth and Cooke[4] reported hematuria, nitrogen retention, and oliguria, with abdominal pain resembling renal colic, in patients receiving sulfapyridine therapy. Actual crystalline sulfapyridine and acetyl sulfapyridine concretions in the urinary tract in humans, established by autopsy, were first noted by Snapper et al.[5] in one patient of a series of four cases showing hematuria during sulfapyridine therapy for pneumonia. Tsao, McCracken, et al.[6] followed with a report of one death due to urinary obstruction with crystalline concretions of sulfapyridine and acetyl sulfapyridine demonstrated at autopsy as obstructing the terminal ureteral orifices.

Case Report

A 70 year old white male was admitted to the University of Michigan Hospital on February 2, 1940 with a history of a chill three days prior to admission. This was followed by profuse sweating, fever, a progressive cough productive of bloody sputum, and pleuritic pain in the left lower chest. The past history revealed an inadequately treated syphilitic infection in 1920, mild "arthritis" of several years' duration, and the removal of a benign cyst of the left kidney in 1928.

On admission the temperature was 103.8 degrees (rectal), pulse 94 per minute, respiratory rate 26 per minute, and blood pressure of 150 mm. of mercury systolic and 70 mm. diastolic. The patient was a well developed and nourished, acutely ill male who appeared to be about the stated age. There was marked facial flushing, excessive perspiration, but no definite cyanosis. The patient was edentulous and the posterior pharynx was hyperemic. Expansion of the chest was limited bilaterally with im-

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paired resonance from the fourth rib downward anteriorly and over both bases posteriorly. In the same areas, tactile fremitus and voice sounds were increased and bronchial breathing was present. Fine moist râles were heard at both bases posteriorly. The heart was not enlarged; the rhythm regular; aortic second sound was slightly accentuated. There was marked abdominal distention and a large, easily reducible umbilical hernia, measuring approximately four by seven centimeters was present. The liver edge was not definitely palpable. Bilateral hydroceles were present. The peripheral arteries were moderately sclerosed.

Chest roentgen-ray, on admission, showed confluent areas of consolidation in both lower lobes of the lungs.

The sputum revealed a Type III pneumococcus reaction by the Neufeld *quellung* method. On admission, the urine was cloudy, acid in reaction, the specific gravity was 1.012 with a 1 + albumin. Microscopic examination revealed no abnormalities. The hemoglobin was 82 per cent (Sahli), the red blood cell count 4.2 million per cubic millimeter, and the white blood cell count 16,100 per cubic millimeter. The differential count showed polymorphonuclear neutrophiles 68 per cent, eosinophiles 1 per cent, lymphocytes 20 per cent, and monocytes 1 per cent. Stool examination showed 1 + guaiac and 4 + benzidene reaction. Blood Kahn test was negative. Blood culture showed no growth.

Immediately after typing and obtaining blood for a culture, sulfapyridine with equal amounts of sodium bicarbonate was administered orally. An initial dose of 3.0 gm. followed by a 1.0 gm. dosage every four hours thereafter was given. At the same time, following sensitivity tests, Type III antipneumococcus rabbit serum (Lederle) was given intramuscularly. A total dosage of 230,000 units was administered within the first eight hours. The temperature, pulse and respirations became normal 18 hours after admission, and remained so thereafter. The course of the patient's illness was uneventful until the evening of the fifth day of hospitalization at which time he became slightly disoriented. He complained of severe left costovertebral angle pain and tenderness. The total amount of sulfapyridine given over the five day period was 33 gm. His fluid intake for the preceding 24 hours was 1625 c.c., whereas the output, over the same period, was 10 + c.c. (The quantity in one specimen was unrecorded, as it was lost with a bowel movement.) At this time the non-protein nitrogen was 40.2 mg. per cent; CO_2 combining power, 48 volumes per cent; and blood sulfapyridine, 15.6 mg. per cent.* The sulfapyridine was discontinued. Catheterization of the bladder produced 15 c.c. of grossly bloody urine, acid in reaction, and containing many crystals. Sulfapyridine determination on this urine specimen gave 83 mg. per cent (free). Ninety minutes later, catheterization was repeated with the same results, and the bladder was irrigated with warm saline solution. Two hours later, cystoscopy was performed by Dr. William G. Gordon of the Department of Urology. The bladder was found to contain 100 c.c. of clear urine, with small amorphous conglomerations of crystalline material of miliary size at the base of the bladder. Depositions of crystalline masses were also visualized about both ureteral orifices, and crystals were seen protruding from the right orifice. Signs of traumatization with increased redness and slight edema were noted about both orifices. Ureteral catheters were passed to the level of the renal pelvis with ease; 10 c.c. of clear urine were obtained from the right kidney pelvis whereas the left contained 30 c.c. of grossly blood-tinged urine. Sediments of both specimens after centrifuging revealed many red cells, and characteristic crystals; the reaction to litmus was acid. Ureteral catheters were left in place and irrigations were done with 10 c.c. of warm saline solution every two hours for 10 hours. At the end of this time the catheters were removed. Fluids by slow continuous intravenous drip were begun immediately after cystoscopy; the urinary output for the 24 hours following cystoscopy was 1,290

* Method of E. K. Marshall, Proc. Soc. Exper. Biol. and Med., 1937, xxxvi, 422; sulfanilamide comparator standards.

c.c. Daily urine examinations continued to show a diminishing microscopic hematuria for five days with complete absence thereafter. The blood sulfapyridine level on February 9, 1940 was 1.3 mg. per cent. Non-protein nitrogen on February 12, 1940 was 38.7 mg. per cent. The patient's subsequent course was uneventful.

Summary

1. A case of Type III pneumonia treated with serum and sulfapyridine is herein reported.

2. Gross hematuria and anuria due to concretions of sulfapyridine were successfully treated by catheterization and irrigation of the ureters.

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HISTOPLASMOSIS: REPORT OF A CASE*

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The fungus infection now known as histoplasmosis, and its causative agent, the *Histoplasma capsulatum*, were first described by Darling in 1906 and 1908.[1, 2] He reported three cases. Since then, single cases of histoplasmosis have been reported by Riley and Watson,[3] Phelps and Mallory,[4] Crumrine and Kessell,[5] and Dodd and Tompkins.[6]

The disease is manifested clinically by moderate fever, emaciation, splenomegaly, hepatomegaly, enlargement of lymph nodes, leukopenia and slight anemia. In only one of the seven cases recorded was an accurate diagnosis made antemortem. Dodd and Tompkins recognized the parasite in the large mononuclear cells (monocytes) of the blood of their patient during life and the diagnosis was confirmed subsequently at necropsy.

On postmortem examination, in addition to the enlargement of the liver, spleen and lymph nodes, areas of necrosis in the liver with cirrhosis, pseudogranulomata of the lungs and of the small and large intestines and focal necrosis

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in the lymph nodes have been noted. In some instances ulcers of the colon occurred. In all cases, the *Histoplasma capsulatum* was readily demonstrable within the endothelial cells of the small lymph and blood vessels of the spleen, liver, lymph nodes, bone marrow, lungs and intestines.

Extensive studies on the morphological characteristics of the parasite were made by da Rocha-Lima [7] in 1912. He regarded it as closely related to, if not identical with *Cryptococcus farciminosus*, the causative organism of epizootic lymphangitis of horses and other solipeds.

Darling was unable either to cultivate the organism in artificial media or to transmit the disease to experimental animals.

DeMonbreun [8] in 1934 first succeeded in cultivating the parasite. Under appropriate conditions he was able to culture it in the yeast-like form as it appears in the lesions, and as a mycelium. He was also successful in reproducing for the first time the characteristic clinical and pathological features of the disease in monkeys, and determined that the pathogenic phase of the fungus is the yeast-like form. These findings were confirmed by Ciferri and Redaelli.[9] DeMonbreun also showed that the yeast-like form of the fungus is pathogenic for mice and puppies.[8]

In this communication an additional case of histoplasmosis is recorded. The diagnosis was established by the histologic examination of a lymph node which was removed one day before the patient died. The case is of particular interest because there was clinical and pathological evidence of co-existing lymphatic leukemia.

Case Report

History: W. W. H., a 56-year-old white farmer who had been a resident of Tennessee all his life was admitted to the Vanderbilt University Hospital, August 13, 1938, complaining of severe sore throat. He had been in excellent health until two years previously when he first noticed small lumps in his neck. These persisted without producing symptoms for about one year when enlargement of the nodes in the inguinal and axillary regions developed. These gradually increased to such size that movements of the limbs became painful and occasioned sufficient difficulty to interfere with the patient's farm work. During the eight months preceding hospitalization he experienced steadily increasing weakness, and he lost 50 pounds in weight. For two months before entering the hospital shortness of breath, intermittent swelling of the ankles and nocturia 2 to 3 times a night occurred, and there were occasional bouts of fever. Three weeks before admission swelling and soreness of his throat developed and caused difficulty in swallowing. Six days before admission he began to cough and expectorated tenacious, foul-smelling, blood-tinged sputum.

Physical examination: On admission to the hospital, his temperature was 102.4° F., pulse 128, respiratory rate 26 and blood pressure 140 mm. of mercury systolic and 96 mm. diastolic. He appeared stuporous but at times was somewhat irritable and restless. The respirations were of the Cheyne-Stokes type. Moderate amounts of tenacious, blood-tinged, muco-purulent sputum were expectorated. His breath and sputum had the foul odor characteristic of fusospirochetal pulmonary infections. His skin was hot, red, dry, and it appeared sun-tanned. There was little subcutaneous fat.

There was marked enlargement of the auricular, occipital, cervical, submaxillary, supra-clavicular, axillary, epitrochlear, inguinal and popliteal lymph nodes. These nodes were tender, rubbery, and freely movable. Most of them were discrete although a few were matted together. The largest masses of nodes were in the inguinal regions and measured about 10 by 5 by 4 cm. The axillary masses measured about 9 by 7 by 4 cm.

The eyes and ears showed nothing remarkable. The nasal mucosa was reddened, swollen and partly covered with a dry hemorrhagic exudate. Marked pyorrhea alveolaris was present and the teeth were carious. The pharynx and the right tonsillar fossa were reddened and edematous. Several large deep ulcers covered by white exudate were present in the pharynx. The soft palate was tensely swollen. The trachea was in the normal position. The sternal dullness was increased several centimeters on each side. A few medium coarse râles were heard at the base of each lung posteriorly. The heart was normal. Several firm, discrete, round, freely movable painless nodules were present in the subcutaneous tissue of the abdomen. The edge of the spleen was palpable one finger's breadth below the costal margin. The liver edge extended one finger's breadth below the right costal margin. No other abdominal masses were felt. Examination of the genitalia, rectum and extremities revealed nothing noteworthy.

Laboratory data: The urine was normal. The red blood cell count was 3,820,000; hemoglobin 11.6 grams; white blood cell count 12,100 with 29 per cent polymorphonuclear neutrophiles and 71 per cent lymphocytes (adult type). The red blood cells showed slight anisocytosis and poikilocytosis, but the hemoglobin content appeared to be normal. The platelets were normal in number and appearance. The Kahn test on the blood was negative. A stool specimen contained no blood, but on microscopic examination from 5 to 10 pus cells per high power field were found; no ova or parasites were seen.

A roentgen-ray of the chest showed an enlargement of the lymph nodes at the hilus of the right lung with some infiltration extending out from the hilus into the lung.

Blood agar plates were inoculated with pharyngeal exudate and incubated at 37° C. for one week. No pathogenic organisms were cultivated. Smears of the pharyngeal exudate revealed many fusiform bacilli and spirochetes. Lymphocytes were present in large numbers, but there were very few polymorphonuclear cells.

Course in hospital: The clinical impression was that the patient suffered from some form of malignant lymphoma, possibly lymphosarcoma. However, the appearance of the pharynx, the high fever, the character of the cervical lymph nodes and the sputum suggested that fuso-spirochetal infection of the pharynx and lung was also present.

During the patient's stay in the hospital there occurred a daily elevation of the temperature to about 103° F. He became delirious. His throat was irrigated with sodium perborate at frequent intervals. Fowler's solution was applied to the pharynx several times daily. He was given one blood transfusion (500 c.c.) and one intravenous injection of neoarsphenamine (0.45 gm.). A roentgen-ray treatment (400 r units) was administered over the left side of the neck. He developed signs of patchy consolidation in the lower lobes of both lungs and expired August 20, 1938, one week after his admission to the hospital.

The diagnosis of histoplasmosis was not made until two days after death. A biopsy of an axillary lymph node obtained on August 15 proved to be unsatisfactory. A cervical node was removed on August 19, one day before death. The sections which revealed the characteristic parasite were not available for study until August 22.

Postmortem examination—Gross: An autopsy was performed two hours post mortem. The body was that of a well-developed, poorly nourished, white male. There was marked enlargement of the auricular, occipital, cervical, submaxillary, supraclavicular, axillary, epitrochlear, inguinal and popliteal lymph nodes. These nodes were soft and discrete and varied in size from about 2 by 2 by 1 cm. to 7 by 4 by 3 cm. The tissue within the capsules of the nodes was soft and very friable. The peritoneal cavity contained no free fluid and the surfaces were free of exudate. No fluid was present in the pleural cavities. The pericardial cavity contained 5 c.c. of clear, straw-colored fluid. The heart weighed 360 grams. No valvular lesions were present. The

right lung weighed 1050 grams, the left lung 530 grams. There was a diffuse pneumonic process throughout the right lung and an abscess 5 cm. in diameter was present near the hilus. The left lung contained several scattered, small areas of consolidation. The liver was enlarged. It weighed 2900 grams. Its surface was smooth and light brown in color. No areas of scarring or necrosis were seen on the cut surface. The spleen was moderately enlarged and weighed 400 grams. The capsule was smooth and the surface was dark purple in color. The pulp was congested and the Malpighian corpuscles were indistinct. The mediastinal, mesenteric and retroperitoneal lymph nodes were enlarged and had the same gross appearance as the superficial nodes. The mesenteric nodes were matted together in a mass weighing 620 grams. The pharyngeal mucosa was the site of several shallow ulcers and its entire surface was of a dirty gray color.

Microscopic: Blocks of tissue were fixed in Zenker's fluid with 10 per cent acetic acid and sections were stained with hematoxylin and eosin. Sections of the cervical, axillary, mediastinal, retroperitoneal, mesenteric and inguinal lymph nodes were studied. The capsules of all the nodes were infiltrated and partly destroyed by numerous small round cells. The normal architecture of the nodes was distorted by the presence of densely packed small lymphocytes. Areas consisting of large mononuclear cells with small nuclei surrounded by abundant pink-staining cytoplasm were present at various points. Within the cytoplasm of these cells were numerous, small, oval or rounded bodies 0.5 to 2 micra in diameter surrounded by refractile non-staining capsules. Usually one or two small masses of dark staining chromatic material were present within the capsule. In the areas of the nodes where the mononuclear cells contained these bodies in greatest abundance there were numerous necrotic foci. Occasional isolated mononuclear cells filled with parasites were scattered throughout the sections. The encapsulated structures within the cytoplasm of the mononuclear cells conformed in every respect to the description given by Darling, DeMonbreun and others of *Histoplasma capsulatum.*

Beside the lesion produced by the parasite the lymph nodes were involved by a process morphologically identical with chronic lymphatic leukemia.

The base of the pharyngeal ulcers consisted of necrotic tissue, fibrin, polymorphonuclear leukocytes, small round cells and masses which appeared to be bacteria. Numerous large mononuclear cells containing the typical parasites of histoplasmosis were present in the submucosa underlying the ulcers and also in the submucosa underlying the intact epithelium. Similar cells containing parasites also infiltrated the adjacent striated muscle. Within the center of dense collections of these cells foci of necrosis were present. There was no ulceration of the epithelium of the epiglottis but the sub-epithelial layer was infiltrated with mononuclear cells, many of which contained parasites.

A diffuse bronchopneumonia with abscess formation was present. Stained smears from the pulmonary exudate contained fuso-spirochetal organisms. *Staphylococcus aureus* was isolated by culture. The spleen and liver showed evidence of chronic lymphatic leukemia but no evidence of parasitic invasion. The adrenals and kidneys were infiltrated with small lymphocytes. No parasites were found within the bone marrow but evidence of chronic lymphatic leukemia was present.

Forty-eight hours after autopsy attempts were made to culture *Histoplasma capsulatum* from the lymph nodes, liver and spleen. The methods described by DeMonbreun [8] were employed. The only organisms recovered were considered to be postmortem contaminants. *Histoplasma capsulatum* was not obtained.

Discussion

The possibility of a fungus infection of the pharynx was considered ante mortem. Cultures on blood agar plates yielded no pathogenic organism. Blood

smears did not reveal the presence of parasites in the leukocytes. The correct diagnosis was not established until two days post mortem when the sections of the lymph node removed during life became available for study. *Histoplasma capsulatum* was promptly recognized, and this led to the delayed and unsuccessful attempts to cultivate the organism from portions of the liver, spleen and lymph nodes.

Microscopic examination showed the *Histoplasma capsulatum* to be present in many lymph nodes in our case, but none were found in the spleen, liver, bone marrow or lungs. The presence of the parasite in the pharynx and epiglottis of our case is noteworthy. Infection in these locations has not been observed in the other cases reported.

Chronic lymphatic leukemia was apparently the primary disease in our patient. The infection with *Histoplasma capsulatum* appears to have been coincidental. In the case reported by Phelps and Mallory [4] histoplasmosis was encountered as a complication in a patient with cirrhosis of the liver and primary liver cell carcinoma. In the remainder of the cases reported, histoplasmosis was the main disease found at autopsy. As in the previously reported instances of this disease no source of the infection could be determined in our patient. This is the second instance of histoplasmosis reported from Tennessee. The case of Dodd and Tompkins [6] was also reported from the Vanderbilt University Hospital and their patient was a resident of this state. It is interesting in this connection that DeMonbreun [10] has recently observed histoplasmosis in a dog in this region.

Summary

A case of histoplasmosis associated with chronic lymphatic leukemia is recorded. This represents the second case of histoplasmosis reported from Tennessee. The diagnosis of histoplasmosis was made by the microscopic examination of a cervical lymph node obtained by biopsy. Postmortem examination revealed an extensive infection with *Histoplasma capsulatum* in the pharynx, larynx and lymph nodes in association with the pathological changes of chronic lymphatic leukemia.

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SIMMONDS' DISEASE (PITUITARY CACHEXIA); REPORT OF A CASE*

By Jason E. Farber, M.D., *Buffalo, New York*

Simmonds' disease or pituitary cachexia is a syndrome ascribed to destruction or physiological exhaustion of the hypophysis (chiefly the anterior portion). The destruction may be caused by embolic infarction, tumor, syphilis, tuberculosis, metastatic abscesses, inflammation, etc. Clinically the Simmonds' syndrome is characterized by cachexia, premature senility, atrophy of the gonads and genitalia, with amenorrhea, atrophy of the breasts, loss of pubic and axillary hair, loss of libido, integumental changes (chiefly dryness of the skin), anorexia and constipation, hypotension and muscular weakness, hypoglycemia, decreased sugar tolerance, lowered basal metabolism and depressed specific dynamic action of proteins, anemia, lymphocytosis and sometimes eosinophilia. These symptoms are believed to be due to the deficiency or absence of the various hormones elaborated by the anterior hypophysis especially the thyrotropic, adrenotropic and gonadotropic hormones.

Since Simmonds' original report [1] of the disease entity which bears his name, approximately 100 reputed cases have been published. Postmortem examinations were not reported in many of these cases, so that confirmation of the pathogenesis was not always satisfactory. In more recent years successful replacement therapy has been reported in a few instances. Having observed for two years a patient on whom a clinical diagnosis of pituitary cachexia was established and on whom subsequently a postmortem examination verified the diagnosis it would seem justifiable to add the case to the literature.

Adequate compilations and bibliographic reviews of Simmonds' disease have appeared in the American and German literature in the past few years. In lieu of repetition attention is directed toward the readily available papers of Silver,[2] Calder,[3] and Graubner.[4]

Case Report

J. B., white, unmarried female, aged 20, of Scotch ancestry, oldest of six siblings, was perfectly well until the age of 14 years, when she noticed difficulty in seeing the blackboard in school. The disturbance in vision increased during the following two years until she could discern only large objects. She also noted difficulty in walking because of frequent stumbling. She was taken to a hospital where a diagnosis of an intracranial lesion was made (pituitary tumor suspected), and seven treatments with deep roentgen-ray were given. These treatments were followed by severe frontal

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From the Buffalo City Hospital and the University of Buffalo Medical School, Buffalo, New York.

headaches. Vision rapidly failed and when seen two and a half years later the patient was totally blind. At this time it was learned that the patient had never menstruated, and had lost 40 pounds (119 to 79) since the onset of the illness. Physical examination revealed an underdeveloped, emaciated girl of 18 years who appeared several years older than the stated age (figure 1). She was nervous, irritable, and rather childish in behavior. There was no light perception in either eye. Due to the blindness a constant "searching type" of nystagmus had developed in each eye. The skin was dry, the scalp hair coarse. There was absence of axillary and pubic hair, and the breasts were barely outlined. The heart, lungs and abdomen were normal. Blood pressure was 80 mm. of mercury systolic and 60 mm. diastolic. The genitalia were infantile.

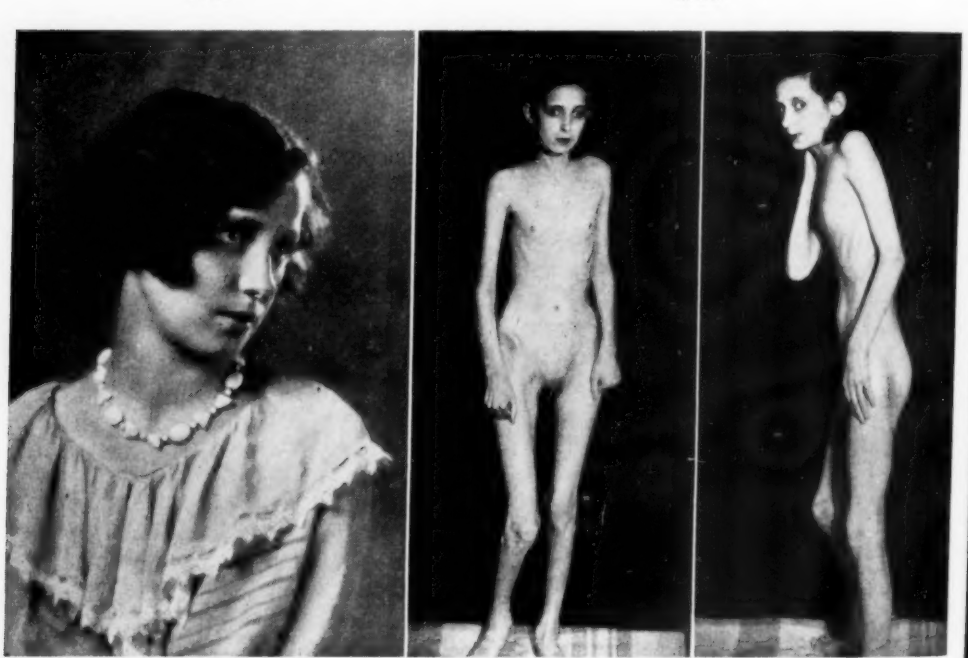

FIG. 1. Photographs of patient in 1928 at age 14 (weight 120 lb.) and in 1934 at age 20 (weight 60 lb.). Note the extreme emaciation characteristic of pituitary cachexia.

Neurological examination showed all the cranial nerves except the optic nerves to be intact. There was generalized muscular weakness of all extremities but no ataxia or paralysis. There were no disturbances of sensory pathways. Reflexes were somewhat hyperactive, but no pathological reflexes were elicited. Anthropometric studies were normal.

Laboratory, roentgen-ray, and special studies were as follows: Blood chemistry: urea 11, 16 mg. per cent; uric acid 3.0, 4.3, 5.0 mg. per cent; creatinine 1.3 mg. per cent; sodium chloride 540 mg. per cent; calcium 10.5 mg. per cent.; inorganic phosphorus 4.6 mg. per cent; CO_2 combining power 59, 60, 67, vols. per cent; cholesterol 68, 72 mg. per cent; sugar 48, 86, 73, 91 mg. per cent. Glucose tolerance test (venous blood), fasting 48 mg. per cent, first hour 147 mg. per cent, second hour 158 mg. per cent. Eleven 24-hour specimens of urine varied in volume from 95 c.c. to 590 c.c. Sodium chloride excretion in three 24-hour collections was 1.05, 0.88, 1.06 gm. Ten single samples of urine showed no abnormalities. The intracutaneous tuberculin test (1:

1000 O.T.) was positive. Gastric contents contained free hydrochloric acid. The Wassermann and Kahn tests were negative. Spinal fluid was clear, contained three cells per cu. mm.; Pandy test was negative; no tubercle bacilli could be isolated. No parasites or ova were found on examination of the feces. Serial blood counts (table 1) showed a normochromic anemia, progressive in character, and a transient relative lymphocytosis. Blood platelets were 210,000 per cu. mm., bleeding time was eight minutes, clotting time five minutes, clot retraction was normal.

TABLE I

Serial Blood Counts of Patient J. B.

Date	Hb. Sahli	R.B.C.	C.I.	W.B.C.	Polymorphonuclears		Eosinophiles	Basophiles	Lymphocytes	Monocytes
					Segmented	Non-Segmented				
1/26/33	73	4,110,000	0.9	5,500	38	7	2	2	47	4
7/20/33	70	3,530,000	0.9	5,500	43	5	4	1	44	3
1/15/34	76	3,790,000	1.0	6,600	48	10	2	2	33	5
4/ 6/34	65	3,020,000	1.0	7,400	51	10	1	1	33	4
6/ 6/34	55	2,650,000	1.0	4,600	38	17	0	0	31	8

Seven separate determinations of the basal metabolic rate varied from minus 25 to minus 41. The specific dynamic action of proteins (Gordon technic) was depressed, showing a change from minus 35 to minus 23 following the protein (difference 12). The control patient showed a change from minus 13 to plus 22 (difference 35) following a similar meal.

The Goetsch adrenalin test was rather striking. Following the injection of 1 c.c. of adrenalin there was an initial rise in systolic blood pressure from 76 to 116 mm. Hg and of the pulse rate from 96 to 132. Both dropped very slowly, not returning to normal until two hours had elapsed. This was in marked contrast with the control patient whose systolic blood pressure and pulse rate returned to normal in nine and five minutes respectively.

Serial roentgenograms of the sella turcica (figure 2) showed progressive enlargement. In July 1930, on a film taken at 30 inches, the sella measured 1.65 cm. in width and 1.3 cm. in depth. There was no erosion of the floor or clinoid processes. In January 1933 the sella measured 1.8 cm. in width and 1.6 cm. in depth. The dorsum sellae appeared thinned, the clinoid processes showed some absorption, and the sella was deeper and wider, the floor of the sella being depressed upon the sphenoidal sinus. In January 1934 the sella measured 2.25 cm. in width and 1.6 cm. in depth. There appeared to be extension of the process anteriorly, producing more widening. In April 1933 roentgenograms of the long bones and spine showed marked osteoporosis but no cystic areas. The epiphyseal lines of the long bones were united, whereas those of the scapulae and clavicles were not. A flat roentgen-ray film of the abdomen showed no evidence of calculi in the kidney regions. Roentgenograms of the chest showed nothing of interest.

Examination of the optic fundi (Drs. Koenig and Freeman) showed bilateral complete optic nerve atrophy, but no evidence of increased intracranial pressure. Examination of the mouth (Dr. S. Koepf) revealed no dental lesions that could be attributed to the pituitary condition. There was no atrophy or hypoplasia of the teeth. Cuspal formation was normal in respect to spacing and height. The clinical diagnosis was Simmonds' disease due to destruction of the pituitary gland by a tumor.

ROENTGEN-RAY OF SELLA TURCICA

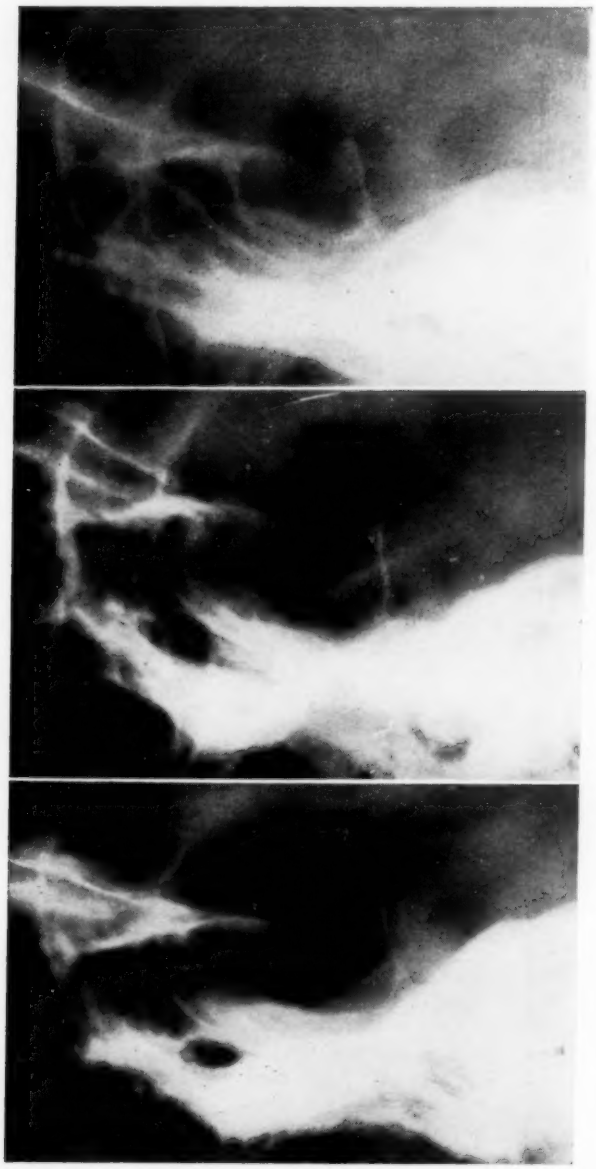

FIG. 2. Roentgen-Ray pictures of the sella turcica showing progressive enlargement caused by the growth of the pituitary tumor.

The clinical course was progressively downhill. The patient was drowsy and slept during the greater part of the day. At times it was necessary to arouse her for meals. She had marked anorexia and frequently refused to eat. However, she was inordinately fond of candy. There was a further loss of weight to 55 pounds. Body temperature ranged from 94° to 98° F., pulse rate from 70 to 80 per minute. The patient's general condition was considered too poor to permit surgery. Replacement therapy with anterior pituitary substance was instituted. Fifty-seven daily parenteral injections of pituitary extract freshly prepared by Professor C. G. MacArthur were given. Results were unsatisfactory. Finally, as a last resort, surgical exploration (Dr. Hamby) of the intracranial cavity was attempted and a tumor was located in the hypophyseal region. The tumor appeared cystic in character and aspiration revealed a gelatinous, sanguineous content. Attempt at removal of the tumor was considered inadvisable. The patient expired two days later. Autopsy was performed by Dr. W. F. Jacobs.

Autopsy Protocol

The body is that of a very slender, emaciated, white female, very pale and anemic in appearance. The external genitalia are infantile, the pubic and axillary hair are absent. The breasts are barely indicated. After removal of the calvarium, the right cerebral hemisphere appears partly collapsed with small fragments of blood clot over the dura which is found incised. After freeing and separating the dura, the convolutions of the cerebral hemispheres, which are markedly flattened, are removed, revealing a multicystic tumor (figure 3) presenting along the incision line, bulging upward chiefly on the right side, but extending definitely to the left of the midline, the cerebral substance being compressed and pushed outward. The under surface of the removed portion reveals circumscribed areas of necrosis with the tumor path upward. The tumor is flaccid and collapsed in part, lying between the temporal lobes and extending forward to a line crossing the tips. Posteriorly it extends to a line limited by the pons. The lateral dimensions of the tumor mass are 4 cm. On its cut surface it measures 4.5 cm. in the anteroposterior and superior inferior aspects. The tumor weighs 82 grams. The cut surface of the tumor reveals a thickened capsule with one large tenacious cavity containing reddish-brown material partly fixed by formalin. Two small pockets measuring 8 by 10 mm. are revealed along the uppermost edge. The contents of these two pockets are gelatinoid. The dura covering the tips of the petrous temporal bone blend with the tumor capsule. The sella turcica is found to be expanded in all directions, thin and partly eroded. Anteriorly it measures 3 cm. and laterally 3 cm. The pituitary is of tissue paper thinness, small, flattened and compressed, lying contiguous with the capsule of the tumor. On separating the bony fragments of the cranial floor from the cystic tumor, the dura found covering the tumor is blended with the dural covering of the sphenoid. The pineal glands appeared slightly larger than usual.

The heart, lungs, liver, pancreas, spleen, kidneys, adrenals, ovaries, Fallopian tubes, and uterus all reveal normal configuration and relations, but are all hypoplastic and remarkably small in size (microsplanchnia). The formalin fixed organs, wiped dry and weighed 24 hours after the autopsy, are as follows: The combined weight of the lungs is 394 grams, the heart 144 grams, the pancreas 64 grams, the spleen 46 grams, the stomach and duodenum 160 grams, the liver 290 grams, the ovaries, tubes and uterus combined 15 grams, the right kidney 43 grams, the left kidney 43 grams, the thyroid 9.6 grams, the pineal bodies 0.4 grams, the adrenals 4 grams.

Histology

Sections of the tumor reveal cysts as is apparent on gross examination with a hand lens. These cysts are lined by epithelial cells, with elongated cytoplasmic proc-

esses. These cyst cell collections at times suggest the picture of an adamantinoma, with the epithelial cells to the periphery and a delicate central reticulum of connective tissue. In none of the tumor sections is keratinization present. Most frequently the cystic areas are large, with an accumulation of fine granular debris, and the epithelial cell element is reduced to a single layer of irregular squamous cells, at times separated from a basement zone of reticulum cells. Some of the larger cysts are confluent. The

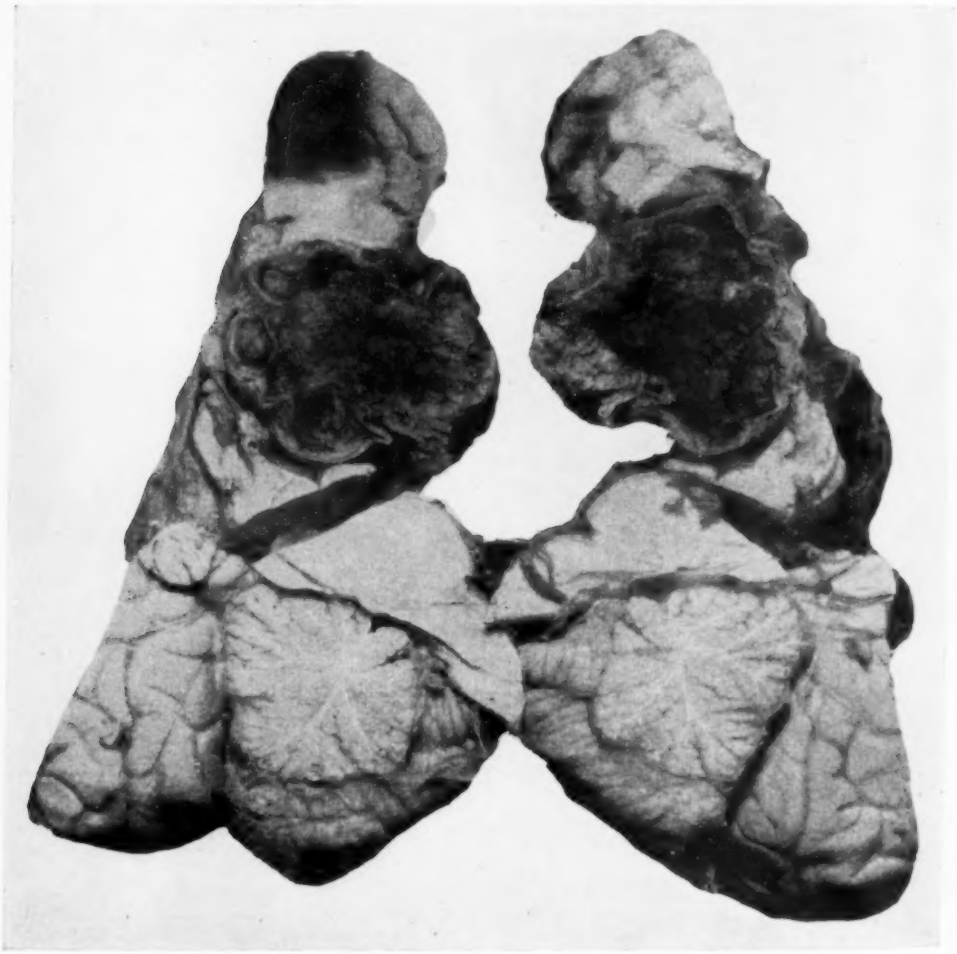

FIG. 3. Photograph of the gross specimen of the cystic pituitary tumor.

bulk of the stroma exhibits smooth muscle fibers and connective tissue, irregularly arranged. Within the meshes are ganglion cell-like structures; these are few and scattered. Also scattered and comparatively few in number are minute duct-like structures lined by a single layer of cells, a homogeneous eosin stained content and a clear zone to the outer side. In this stroma of connective tissue there are a few intervening patches of an embryonic form of connective tissue. There are fairly well defined arteries, arterioles, and capillaries.

The extrasellar location of the tumor and its relation to the pituitary, the epi-

thelial lined cystic cavities, the epithelial cell rests, and the absence of metastasis and infiltrative extension mark it as a histologically benign pituitary stalk tumor.[5]

On section of the remains of the hypophysis no abnormality is noted; the cells are well differentiated and proportioned. The abdominal thoracic organs on routine histological study do not reveal any features of unusual interest. There is moderate hyaline degeneration of the arteries of the heart muscle. The adrenals are normal. Section of the pancreas reveals an accumulation of zymogen granules in the gland cells. Sections of the thyroid exhibit large collections of lymphocytes in the stroma, the colloid is homogeneous and evenly stained, the lining cells are low columnar and well defined. The capsules of the kidney are thickened by fibrosis. Anatomical diagnosis: Pituitary stalk tumor (cystic epithelioma); pituitary, optic nerve and cerebral compression; microsplanchnia; emaciation; craniotomy.

Discussion and Summary

The significant clinical symptoms and signs were cachexia, blindness, loss of axillary and pubic hair, atrophy of breasts and genitalia, amenorrhea, asthenia, anorexia and constipation, integumental changes, hypotension, hypothermia, oligodipsia, oliguria, mental changes and pathological sleep. Laboratory studies showed a lowered basal metabolic rate, lowered or depressed specific dynamic action of proteins, hypoglycemia, decreased glucose tolerance, hypocholesterolemia, hypochloremia and hypochloruria, anemia and relative lymphocytosis, disturbed water and salt balance. Anthropometric studies did not show any deviation in bony measurements from the normal.

Not all of these abnormalities, of course, are a feature of destruction of the pituitary. It was felt that the mental changes, pathological sleep, hypothermia, disturbances in water and salt balance, and the blindness were probably due to injury by the expanding tumor onto surrounding structures, especially the optic nerves and hypothalamus.

Replacement therapy and exploratory craniotomy were unsuccessful. At autopsy a pituitary stalk tumor (cystic epithelioma) was found. There was generalized microsplanchnia of all organs.

The writer wishes to express appreciation to Professor C. G. MacArthur for the pituitary extracts, to Dr. W. F. Jacobs for the autopsy material, and to both for their kind advice and suggestions.

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EDITORIAL

CONTROL OF THE DOSAGE OF ANTIPNEUMOCOCCAL SERUM IN THE TREATMENT OF PNEUMONIA

Since effective antipneumococcal sera first became available for the treatment of acute lobar pneumonia the need of some precise method for determining the quantity of serum required has been evident. Attempts have been made to estimate this by considering such factors as the day of the disease on which treatment is started, the extent of the lung tissue affected, the presence or absence of bacteremia and the apparent degree of intoxication, as well as the clinical response to treatment. Although these points are of considerable assistance in the absence of more precise standards, experience soon showed that they are not satisfactory and that in individual cases they may be seriously misleading. In some cases, although a fall in temperature, arrest of the process in the lungs and symptomatic improvement seemed to indicate that sufficient antiserum had been administered, the disease has later relapsed and progressed to a fatal termination. In other cases, persistent fever and failure to improve clinically have been found later to be due to focal complications such as empyema, sterile pleural effusions, arthritis or endocarditis, conditions which ordinarily cannot be cured by an excess of serum.

The desirability of giving amounts of serum sufficient to neutralize all of the specific polysaccharide in the tissues is obvious. On the other hand, it is important practically to avoid a gross excess of serum, both because of its high cost and because of its tendency to increase the frequency and exaggerate the intensity of serum disease.

The fact that the effectiveness of antipneumococcal serum is probably due to its antibody content, as measured by its protective power for mice and less precisely by its agglutinin content, led Sabin [1] to utilize the appearance of agglutinins in the patients' blood as an indication that sufficient serum had been administered. It was soon shown that agglutinins may appear before sufficient serum has been administered to bring about recovery. Attempts by Bullova [2] to utilize a quantitative modification of this method, and by Bullova and Sharff [3] to use a modification of Neufeld's "quellung" reaction proved unsatisfactory for the same reason.

Tillet and Francis [4] found that patients convalescent from pneumonia would give a positive skin reaction to the intradermal injection of a minute amount of the highly purified homologous capsular polysaccharide. The

[1] Sabin, A. B.: The microscopic agglutination test in pneumonia; its application to rapid typing and control of serum therapy, Jr. Infect. Dis., 1930, xlvi, 469.

[2] Bullova, J. G. M.: The management of the pneumonias, 1937, Oxford University Press, New York.

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[4] Tillet, W. S., and Francis, T., Jr.: Cutaneous reactions to the polysaccharides and proteins of pneumococcus in lobar pneumonia, Jr. Exper. Med., 1929, i, 687.

reaction consisted of a wheal and an erythematous flare appearing within 10 to 30 minutes and fading within one to two hours. The reaction did not appear until recovery was under way, and was always associated with the presence of antibodies (agglutinins and protective substances) in the blood. It remained negative in fatal cases, even though antibodies could sometimes be demonstrated in the serum. Francis [5] reported a study of the test in 48 cases of Type I pneumonia treated with antiserum. He regarded it as superior to the agglutination test as a guide to treatment and emphasized the fact that a positive reaction depends not only upon the presence of antibodies in the blood serum, but also upon the reactivity of the skin. The latter is lacking in gravely ill cases running an unfavorable course. "When positive it invariably denotes that recovery has begun, when negative it indicates further serum therapy."

Francis' observations were confirmed by MacLeod, Hoagland and Benson.[6] Finland [7] and Bullova and Sharff,[3] on the other hand, did not find the skin test entirely dependable. More recently, however, Wood [8] has reported a careful study of the test, and its use in 51 cases of pneumonia treated with serum. Serum was given in large doses at short intervals until an unquestionably positive reaction was obtained. It was then stopped, without regard to the clinical condition of the patient. The quantity required varied from 11,000 to 1,983,000 units. Such differences could not have been foreseen or estimated by any rule of thumb. In general, he fully confirms Francis' observations as to the characteristics of the test and as to its value as a guide in prognosis and treatment. Every patient who recovered developed a positive skin test except one case—a negro—in whom it was impossible to make a reading. His observations indicate that the reaction is due to a combination of specific polysaccharide and antibody in the skin. He also found that in severely ill patients the skin may fail to react, even though both substances are present; or that a reaction which has been positive may become negative. In four of five such cases, however, additional serum restored a positive reaction and recovery occurred.

There are some limitations which must be observed in the interpretation of the test. It is essential that the solution of polysaccharide used for testing be pure. Contamination with a trace of protein or other materials is likely to cause nonspecific skin reactions which destroy the value of the test. In five cases, for unknown reasons, a positive skin reaction was obtained early

[5] Francis, T., Jr.: The value of the skin test with type specific capsular polysaccharide in the serum treatment of type I pneumococcus pneumonia, Jr. Exper. Med., 1933, lvii, 617.

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Ibid.: II. The clinical application of the Francis skin test, Jr. Clin. Invest., 1940, xix, 105.

in the disease before the serum had been administered and before antibodies were demonstrable in the serum. The procedure is manifestly of no value in such cases, and if it is to be used as a guide to treatment, a negative test must be obtained before any serum is administered. In three cases a positive reaction was present shortly before death. This was owing in one case to pneumococcal meningitis; in one to pneumococcal endocarditis; and in one to uremia, after apparent recovery from the pneumococcal infection. Persistent fever and clinical illness after the skin test became positive usually meant some complicating focal infection, most often an empyema or a sterile pleural effusion, which demands surgical treatment and will not be influenced by further intravenous administration of serum. In one case it was owing to a recurrent pneumonia caused by a different type of organism.

The test also proved satisfactory in eight cases receiving both sulfapyridine and serum.

More work is obviously necessary to determine precisely the limitations of the test. It promises to be of great practical value in that in most cases, at least, it is a dependable guide as to the amount of antipneumococcal serum required, and as to the outlook for recovery. In many cases, also, it may suggest the existence of some focal, complicating infection.

The use of sulfapyridine has greatly restricted the need for serum therapy in pneumonia. There are, however, some patients who can not take sulfapyridine because of its toxicity. In a few cases sulfapyridine is ineffective (Long and Wood).[9] Experience may still show that a combination of serum and sulfapyridine is more effective than either alone. There will remain a definite, if relatively circumscribed, field for the use of serum, and the test is apparently applicable to such cases.

P. C.

[9] Long, P. H., and Wood, W. B.: Observations upon the experimental and clinical use of sulfapyridine. II. The treatment of pneumococcal pneumonia with sulfapyridine. Ann. Int. Med, 1939, xiii, 487.

REVIEWS

Handbook of Hematology. In 4 volumes. Vol. 3. Edited by HAL DOWNEY, Professor of Anatomy, Medical School, University of Minnesota, Minneapolis. Thirty-seven contributors. 3136 pages. 1448 illustrations, including 50 colored plates. Paul B. Hoeber, Inc. (Medical Book Department of Harper Brothers), New York. 1938. Price, $85.00 set. Volume three, pages 1587–2360.

The third volume of the Handbook of Hematology contains 13 sections, the contents of which are approximately equally divided between discussions of various hematological disease entities and morphological and pathological data concerning various parts of the hemolytopoietic system. Thus there are chapters on the spleen, hemolymph nodes, bone marrow, the myeloblasts and myeloid metaplasia as well as individual sections on classification of the anemias, aplastic anemia, pernicious anemia, chronic hereditary hemolytic jaundice, sickle cell anemia, and ovalocytosis. The scholarly approach to each subject, noted in previous volumes, is apparent here also. The voluminous bibliographies appended to each chapter are especially worthy of comment since they are extremely helpful to the worker in this field.

The monographic proportions of many of the chapters invite individual comment in some instances. In the section on the spleen the embryology, anatomy, and pathology are exceedingly ably covered, but it appears to the reviewer that a more detailed consideration of the physiologic data with reference to this viscus would have been extremely helpful. The several sections devoted to a consideration of normal and pathological bone marrow structure are a source of information unrivaled in the English or American literature. The existence of the myeloblast, its cytological characteristics, its possible identity with the lymphoblast, and evidence for its being the stem cell for hemocytes arising in the marrow are presented in a very illuminating and beautifully illustrated section by Downey. The reviewer, however, cannot but take exception to some of the views presented in the chapter on classification of anemias. The author presents an etiological classification in which, for example, the anemia associated with leukemia is placed in a category of "sequelae of toxic conditions." This apparently negates the influence of the hemorrhagic manifestations of many acute leukemias and the myelophthisic process associated so often with chronic leukemia. Nor does it seem rational for a morphological classification to separate various types of anemia on the basis of whether they show anisocytosis or poikilocytosis. The section on pernicious anemia presents many valuable data, but it is rather disappointing to find the neurological aspects of this disease dismissed with only five or six lines of comment.

With the exception of these inadequacies, culled from a volume of approximately eight hundred pages, the bulk of the material gathered together in this volume represents a contribution to the field of hematology which is invaluable.

M. S. S.

The Compleat Pediatrician. By W. C. DAVISON, M.D. 250 pages; 24 × 16 cm. Duke University Press, Durham, North Carolina. 1938. Price, $3.75.

One is perhaps most impressed by the very clever arrangement of "The Compleat Pediatrician." Only after a study of the rather simple instructions for its use can the book be fully appreciated.

Its outstanding purpose is its aid in diagnosis, which is accomplished by a grouping of symptoms. The symptoms and diseases have been arranged into seven chapters on the basis of the anatomical system most often involved. Each of the chapters starts

with a list of symptoms and signs involving that particular system, together with a list of the diseases which cause them most frequently.

That "The Compleat Pediatrician" is of value as a quick reference there can be no doubt, since it contains a wealth of information gleaned from extensive investigation of recent literature. Chapters on treatment, medications, laboratory, nutrition, growth and development are also present.

It is the reviewer's opinion that the book is especially useful to the general practitioner as a quick reference, but decidedly less important to one specially trained in pediatrics. Many of the descriptions of diseases must through necessity be so brief that they leave a sensation of thirst that remains unquenched.

W. M. S.

Proctology for the General Practitioner. By FREDERICK C. SMITH, M.D., M.S.C., (Med.), F.A.P.S. 386 pages; 23.5 × 15.5 cm. F. A. Davis Company, Philadelphia. 1939. Price, $4.50.

For the general practitioner with limited time at his disposal, this book affords an opportunity to acquire some knowledge of recent advances and generally accepted principles in proctologic practice. Much shorter than the usual work on the subject, it lays particular stress upon diagnosis and diagnostic methods along with such minor operative procedures as can be performed in the office. Sclerotherapy and injection methods for the relief of symptoms are dealt with adequately and in their true perspective. Anesthetic methods receive more than the usual attention. Operations for hemorrhoids, fissure, fistula are given in detail but the more extensive surgical procedures are only concisely described. The inclusion of a chapter on the commoner intestinal parasites is a welcome feature. The illustrations are largely by the author but he has also used cuts from standard textbooks, wherever they appeared to be helpful. For those who want their information in concentrated form, this book will suffice.

M. E.

Doctors on Horseback. By JAMES THOMAS FLEXNER. 359 pages; 22 × 15 cm. The Viking Press, New York. 1937. Price, $2.75.

Students of American history as well as students of medical history will be equally attracted by this book. The pioneer physicians of America established the medical profession and its institutions, encountered a revolutionary war with all its medical problems, and in addition, made lasting fundamental contributions to medical knowledge. Speaking of the debt owed the pioneers of medicine by the modern physicians, the author in his Foreword says, "—in the settlements of a new nation there appeared doctors of genius, explorers who, without laboratories or instruments of precision or even any formal training, made great discoveries that helped usher in the age of modern medical science. The modern physician, with all his varied resources, follows the trails these half-forgotten pioneers have blazed."

The medical men of the American Revolution are well represented by chronicles of John Morgan and Benjamin Rush. The story of Ephraim McDowell, the "father of ovariotomy," is interestingly told. The first medical student in Cincinnati and later the great physician of the Mississippi Valley was Daniel Drake. His life story as told in this book is most absorbing. The book also contains one of the most romantic stories of pioneer medicine, the story of William Beaumont who became one of the world's greatest physiologists. In the "ether controversy" which continues today, the author suggests an amicable settlement by proposing to give credit to both William T. G. Morton and Crawford W. Long as almost simultaneous discoverers of anesthesia.

Numerous source documents are quoted in which the author has modernized the

spelling and punctuation. The author does not hesitate to lay bare the true state of affairs as revealed by the source material which he searched.

There are an excellent bibliography and index. It is unusual that one finds accurate history told with absorbing interest, and even though written in separate sections the book seems an integrated whole to the absorbed reader.

J. E. S.

Diagnostic Signs, Reflexes and Syndromes (Standardized). By WILLIAM EGBERT ROBERTSON, M.D., F.A.C.P., and HAROLD F. ROBERTSON, B.S., M.D., F.A.C.P. 309 pages; 18 × 12.5 cm. F. A. Davis Company, Philadelphia. 1939. Price, $3.50.

This book presents a new departure in medical collation. The authors have gathered and codified an amazing number of signs, reflexes, and syndromes. Where confusion existed they trace sources back to authorities and briefly mention pertinent facts. Throughout the compend-size volume are many cross references, no index. The style is pleasantly modern. As far as this reviewer's knowledge goes, no gross misstatements of fact nor departures from usually accepted terminologies are to be found. There is a gratifying freedom from typographical errors. Nightly perusal is recommended to all medical people, because of surprising and little known facts which will be revealed about signs and symptoms of everyday use and interest.

C. A.

COLLEGE NEWS NOTES

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. George C. Griffith, Philadelphia, Pa.
Dr. Maud L. Menten, Pittsburgh, Pa.

Gifts to the College Library

We gratefully acknowledge receipt of the following books donated to the College Library:

"Graduate Medical Education in the United States: I—Continuation Study for Practicing Physicians, 1937 to 1940" from the Council on Medical Education and Hospitals of the American Medical Association;
"Dr. Lawrence F. Flick—1856–1938" from the White Haven Sanatorium Association.

The following gifts to the College Library of publications by members are gratefully acknowledged:

Reprints

Dr. J. G. Archer, F.A.C.P., Greenville, Miss.—2 reprints;
Dr. J. Edward Berk (Associate), Philadelphia, Pa.—5 reprints;
Dr. Philip G. C. Bishop (Associate), New York, N. Y.—1 reprint;
Dr. Belford C. Blaine (Associate), Pottsville, Pa.—"Minutes of the Commission on Diabetes, October 3, 1939";
Dr. William Ramsey Blue (Associate), Memphis, Tenn.—1 reprint;
Dr. Leon L. Blum (Associate), Terre Haute, Ind.—5 reprints;
Dr. Verne S. Caviness, F.A.C.P., Raleigh, N. C.—6 reprints;
Dr. Walter Clarke, F.A.C.P., Caldwell, N. J.—1 reprint;
Dr. Samuel Cohen (Associate), Jersey City, N. J.—7 reprints;
Dr. Frederic G. Dorwart, F.A.C.P., Muskogee, Okla.—1 reprint (in duplicate);
Dr. Joseph F. Elward (Associate), Washington, D. C.—1 reprint;
Dr. Robert H. Felix (Associate), Lexington, Ky.—1 reprint;
Dr. A. Allen Goldbloom, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—10th, Second Series, Supplement to "Modern Drug Encyclopedia and Therapeutic Guide";
Dr. Lynn T. Hall, F.A.C.P., Omaha, Nebr.—2 reprints;
Dr. Elmer Highberger, Jr. (Associate), Greensburg, Pa.—1 reprint;
Dr. Clifton K. Himmelsbach (Associate), Lexington, Ky.—1 reprint;
Dr. Morrill L. Ilsley, F.A.C.P., Claremont, Calif.—1 reprint;
Dr. William H. Kraemer, F.A.C.P., Wilmington, Del.—1 reprint;
Dr. Michael Lake, F.A.C.P., New York, N. Y.—5 reprints;
Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—"Ninth Annual Report of the Tuberculosis Committee, American Student Health Association";
Major H. P. Marvin, (MC), USA., F.A.C.P., Washington, D. C.—2 reprints;
Dr. Oliver T. Osborne, F.A.C.P., New Haven, Conn.—1 reprint;

Dr. H.D. Piercy, F.A.C.P., Cleveland, Ohio—1 reprint;
Dr. B. S. Pollak, F.A.C.P., Jersey City, N. J.—1 reprint;
Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J.—2 reprints;
Dr. Robert M. Stecher, F.A.C.P., Cleveland, Ohio—13 reprints;
Dr. Frederick R. Taylor, F.A.C.P., High Point, N. C.—1 reprint.

Regional Meeting of Florida Members

A regional meeting of the Florida members of the American College of Physicians was held at Tampa, Fla., on April 29, under the chairmanship of Dr. William C. Blake, F.A.C.P., Tampa, with Dr. Kenneth Phillips, F.A.C.P., Miami, as secretary. The meeting preceded the opening of the 67th annual meeting of the Florida Medical Association.

The morning was given over to a scientific session, program for which was as follows:

"Theories of Renal Function," Dr. James A. Bradley, F.A.C.P., St. Petersburg;
"Case Report—An Unusual Case of Tuberculosis in a Ten Year Old Girl," Dr. Douglas D. Martin, F.A.C.P., Tampa;
"Functional Heart Disease," Dr. Norval M. Marr, F.A.C.P., St. Petersburg;
"Death From Insulin Shock with Autopsy," Dr. H. Mason Smith, F.A.C.P., Tampa.

Members joined in the discussion of each paper. There was a luncheon meeting at noon addressed by Dr. T. Z. Cason, F.A.C.P., College Governor for Florida, Dr. Charles H. Cocke, F.A.C.P., Chairman of the Board of Governors, Asheville, N. C. and by Mr. E. R. Loveland, Executive Secretary of the College, Philadelphia. Dr. Cocke discussed the objectives of the College and the requirements for membership and Mr. Loveland discussed the activities of the College and the operation of the executive offices. Present at the meeting and the luncheon were eight guest physicians from Havana, Cuba, most of whom occupy important teaching positions in Internal Medicine or allied subjects at the University of Havana. General interest was expressed in the extension of the College membership to Cuba, with the selection of the most outstanding internists there. Present at the meeting were approximately forty of the members of the College from Florida, out of a total membership of sixty.

The regional meeting for 1941 will be held in Jacksonville. Dr. Louie Limbaugh, F.A.C.P., Jacksonville, was selected as chairman and Dr. Kenneth Phillips, F.A.C.P., Miami, was reëlected secretary.

Rhode Island Regional Meeting

On April 13 the Fellows and Associates of the American College of Physicians of Rhode Island held a regional meeting at the Rhode Island Hospital. Dr. C. F. Gormly, Physician-in-Chief of the Medical Department of the Hospital presided. The speakers were Drs. H. A. Lawson, Louis I. Kramer, Russell S. Bray, C. F. Gormly and A. M. Burgess, Fellows, and Dr. F. H. Chafee, Associate.

Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., spoke before the Des Moines Academy of Ophthalmology and Otolaryngology on the subject of "Allergy in Rhinology," March 25. Dr. Feinberg also held a clinic on allergy and gave a talk on the subject of "Summer Allergy" at the meeting of the Eleventh Indiana Councilor District Medical Association, on May 15, at Huntington, Ind.

The decennial meeting of the Convention for the revision of the Pharmacopoeia of the United States was held in Washington, D. C., May 14–15, 1940, under the presidency of Dr. Walter A. Bastedo, F.A.C.P., New York, N. Y.

The delegates of the American College of Physicians at this Convention were Dr. Charles F. Tenney, F.A.C.P., New York, N. Y., Dr. Torald Sollmann, F.A.C.P., Cleveland, Ohio, and Dr. Edward Dean Spalding, F.A.C.P., Detroit, Mich.

The Seventh Annual Post-Graduate Conference of the staff of the Mercy Hospital, Wilkes-Barre, Pa., was held on April 25. Guest speakers of this meeting were: Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, Pa., who spoke on "Diabetes as a Complication of Other Diseases" and Dr. M. Herbert Barker, F.A.C.P., Chicago, Ill., who spoke on "The Ionic Control of Edema." During the evening there was a regional meeting of the Commission on Diabetes. Dr. Belford C. Blaine (Associate), Pottsville, Pa., Chairman of the Commission on Diabetes, and Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, Pa., presided. The topic of discussion was "Lay Education on Diabetes."

The New York Cardiological Society held their regular stated meeting April 24, at the New York Academy of Medicine. Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, Pa., presented a paper on "Some of the Unsolved Problems in Electrocardiography," which was discussed by Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.

Dr. Ralph C. Matson, F.A.C.P., Portland, Ore., has been appointed Chief Surgeon of the University State Tuberculosis Hospital in Portland.

On April 3 Dr. Matson addressed the Oregon Tuberculosis Association in Bend, Ore., on "Modern Trends in the Surgical Treatment of Pulmonary Tuberculosis." On April 5 he held a surgical clinic in the University State Tuberculosis Hospital for the Pacific Coast Surgical Society.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "Diet and Nutrition in Nephritis" at the recent Fifth Annual Postgraduate Institute of the Philadelphia County Medical Society. Dr. Kelly also presented an exhibit on "Deficiency Disease" at this meeting.

On April 12 Dr. Kelly addressed the Seventh Councilor District of the Medical Society of the State of Pennsylvania in Williamsport, Pa., on "Healthful Living."

The American College of Chest Physicians under the Presidency of Dr. Ralph C. Matson, F.A.C.P., Portland, Ore., will hold its Sixth Annual Meeting in New York, N. Y., June 8–10, 1940. Dr. George Ornstein, F.A.C.P., New York, N. Y., is General Chairman of the Scientific Program Committee; Dr. Foster Murray, F.A.C.P., Brooklyn, N. Y., is Chairman of the Medical Section; Dr. David Ulmar, F.A.C.P., New York, N. Y., is Chairman of the Surgical Section; Dr. Edward P. Eglee, F.A.C.P., New York, N. Y., is Chairman of the Clinical Section; and Dr. Edgar Mayer, F.A.C.P., New York, N. Y., is Chairman of the General Arrangements Committee. Among the features of this meeting will be two "Information Please" Luncheons. At these luncheons experts in tuberculosis will conduct round table discussions and answer various questions previously submitted. Among those who will participate in these luncheons are Dr. James Alex. Miller, F.A.C.P., New York, N. Y., Dr. Ralph C. Matson, F.A.C.P., Portland, Ore., Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill., and Dr. Carl R. Howson, F.A.C.P., Los Angeles, Calif.

Twelve other Fellows and two Associates of the College will participate in the formal program of this meeting and will present papers.

Among those who will speak before the Section on Medicine of the Medical Society of New Jersey at their meeting in Atlantic City, June 4–6, will be the following:

Dr. Ralph K. Hollinshed, F.A.C.P., Westville, N. J.
Dr. Thomas K. Lewis, F.A.C.P., Camden, N. J.
Dr. Benjamin Saslow (Associate), Newark, N. J.
Dr. Sydney R. Miller, F.A.C.P., Baltimore, Md.
Dr. Aaron Parsonnet, F.A.C.P., Newark, N. J.
Dr. Thomas M. Kain, F.A.C.P., Camden, N. J., is Chairman of this Section.

The Fifth Annual Convention of the National Gastroenterological Association will be held in New York, N. Y., at the Hotel Roosevelt, June 4–6. Among those who will participate in this program are the following:

Dr. Anthony Bassler, F.A.C.P., New York, N. Y.
Dr. Samuel Weiss, F.A.C.P., New York, N. Y.
Dr. Clarence J. Tidmarsh, F.A.C.P., Montreal, Que., Can.
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.
Dr. Henry A. Rafsky, F.A.C.P., New York, N. Y.
Dr. Hyman I. Goldstein (Associate), Camden, N. J.
Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J.
Dr. Manfred Kraemer, F.A.C.P., Newark, N. J.
Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y.

Dr. Roland A. Davison, F.A.C.P., Tucson, Ariz., was one of the speakers at the annual meeting of The Arizona Hospital Association in Phoenix. The subject of Dr. Davison's address was "The Importance to Hospitals of Good Public Relations Education."

Dr. James E. Paullin, F.A.C.P., and Dr. Cyrus W. Strickler (Associate), both of Atlanta, Ga., were among those who presented a symposium on the problems of medical care in Georgia, at the annual meeting of the Medical Association of Georgia, held at Savannah April 23–26. Dr. Kenneth M. Lynch, F.A.C.P., Charleston, S. C., gave an address on "Progress in Knowledge and Control of Cancer" at this meeting.

Dr. Christian B. Luginbuhl, F.A.C.P., Des Moines, Iowa, has been appointed to the newly established library board of the Iowa Methodist Hospital. Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa, recently donated 225 volumes to this library.

Dr. Elston L. Belknap, F.A.C.P., Milwaukee, Wis., was one of the speakers who addressed the annual meeting of the Michigan Association of Industrial Physicians and Surgeons on April 17 in Grand Rapids, Mich. The subject of Dr. Belknap's address was "Silicosis—Wisconsin Plan."

Among those who addressed the recent annual meeting of the Missouri-Kansas Neuropsychiatric Association in Kansas City, Mo., were:

Dr. Walter Freeman, F.A.C.P., Washington, D.C.—"The Wincing Reaction";
Dr. George T. Harding, F.A.C.P., Columbus, Ohio—"The Treatment of Psychiatric Patients in the Private Hospital."

Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., addressed the Kansas City Academy of Medicine, April 19, on "Chemotherapy in Respiratory Diseases."

Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, Md., addressed a meeting of the Broome County Medical Society at Binghamton, N. Y., March 12, on "Hypertension, Its Clinical Significance and Treatment."

Dr. Lay Martin, F.A.C.P., Baltimore, Md., was one of those who addressed the New York chapter of the National Gastroenterological Association March 18. The subject of his address was "Prolonged Partial Obstruction of the Small Intestine."

Dr. Mark A. Griffin, F.A.C.P., Asheville, N. C., was elected President of the North Carolina Neuropsychiatric Society at their recent meeting in Charlotte, N. C.

President-elect Roger I. Lee, F.A.C.P., Boston, Mass., addressed the Columbia Medical Society (S. C.), March 11, on hypertension.

Dr. George R. Wilkinson (Associate), Greenville, S. C., was one of those elected vice president of the Tri-State Medical Association of the Carolinas and Virginia at the annual meeting in Richmond, February 26–27.

On April 25, Dr. Burt R. Shurly, F.A.C.P., Detroit, Mich., was presented with a gold medal, which had been awarded him by the American Academy of Ophthalmology and Otolaryngology at its 1939 annual session for noteworthy contributions to the knowledge of nose and throat disorders. Presentation of this medal was made at a testimonial dinner in Detroit in honor of Dr. Shurly.

Among those who spoke at the annual meeting of the Society for the Study of Asthma and Allied Conditions in Atlantic City, N. J., April 29, were:

Dr. Robert A. Cooke, F.A.C.P., New York, N. Y.—"Sensitizations Induced by Tetanus Toxoid";
Dr. George Piness, F.A.C.P., Los Angeles, Calif.—"Relationships Between Foods as Shown by the Skin Test in 1,000 Children";
Dr. Louis E. Prickman, F.A.C.P., and Dr. Herman J. Moersch, F.A.C.P., both of Rochester, Minn.—"The Diagnosis and Treatment of Bronchostenosis, an Important Complication of Asthma."

Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa, was reëlected secretary of the Federation of State Medical Boards of the United States at their recent meeting in Chicago, Ill.

Dr. Samuel R. Haythorn, F.A.C.P., Pittsburgh, Pa., was elected vice president and Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio, was elected secretary of the American Association of Pathologists and Bacteriologists at their annual meeting in Pittsburgh, Pa., on March 21.

The Walter Jarvis Barlow Society of the History of Medicine recently created a lectureship in honor of Dr. George Dock, F.A.C.P., Pasadena, Calif. Dr. Dock presented the first lecture at a dinner in his honor. The subject of his address was "A Dictionary of Medical Biography."

The following Fellows of the College spoke at the sixty-first annual meeting of the Louisiana State Medical Society held in New Orleans, April 22–24:

Dr. Byrl R. Kirklin, Rochester, Minn.—"Solving Problems in the Diagnosis of Diseases of the Lungs";
Dr. John H. Musser, New Orleans, La.—"Typhus Fever in Louisiana";
Dr. Daniel N. Silverman, New Orleans, La.—"Early Diagnosis and Treatment of Amebic Abscess of the Liver."

At the eighty-third annual session of the Missouri State Medical Association held in Joplin, Mo., April 29–May 1, the following Fellows of the College participated:

Dr. Cyrus C. Sturgis, Ann Arbor, Mich.—"Prognosis and Treatment of Hypertension";
Dr. John H. Musser, New Orleans, La.—"Treatment of Some of the Contagious Diseases";
Dr. Nathan B. Van Etten, New York, N. Y.—"An American Health Program."

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, delivered the tenth course of lectures under the Porter Lectureship in Medicine of the University of Kansas. On April 30 he lectured on "Hemolytic Anemia" and on May 1, on "The Red Blood Cell of Man" and "Polycythemia."

Dr. George R. Herrmann, F.A.C.P., Galveston, Texas, was the speaker at a joint meeting of the St. Louis Medical Society and the St. Louis Clinics, during the annual postgraduate course and clinical conference of the St. Louis Clinics, held in St. Louis, Mo., May 14. The subject of Dr. Herrmann's address was "Recognition and Management of the Common Circulatory Emergencies."

At the annual meeting of the Medical Society of the State of New York, held in New York City, May 6–9, Capt. Harry G. Armstrong, (MC), U.S.A. (Associate), spoke on "General Medical Problems in Aviation" and Lieut. Col. William D. Fleming, (MC), U.S.A., F.A.C.P., spoke on "Medical Problems in Aviation."

On April 4 Dr. Paul Dudley White, F.A.C.P., Boston, Mass., delivered the fifteenth Hermann Michael Biggs Memorial Lecture of the New York Academy of Medicine. The subject of Dr. White's lecture was "Heart Disease—A World Problem."

On May 1 Dr. Thomas Addis, F.A.C.P., San Francisco, Calif., delivered the Adam M. Miller Memorial Lecture at the Long Island College of Medicine, Brooklyn, N. Y. The subject of his address was "The Anatomical and Physiological Concepts Underlying the Treatment of Glomerular Nephritis."

Dr. Oscar W. Bethea, F.A.C.P., New Orleans, La., was one of the guest speakers at the ninety-second annual meeting of the South Carolina Medical Association in Charleston, April 30–May 2.

At this meeting Dr. Robert Wilson, F.A.C.P., Dean of the Medical College of the State of South Carolina, was presented with the distinguished service plaque by the American Legion.

OBITUARIES

ALFRED JAMES SCOTT

Dr. Alfred James Scott, F.A.C.P., of Los Angeles died at his home on the seventeenth of April of coronary disease. From the first attack four years ago he had led a restricted existence. Dr. Scott was born in Michigan, September 28, 1881. He came to Los Angeles as a young man and was a telegraph operator prior to and while he was studying medicine at the Southern Branch of the University of California from which he was graduated in 1909. He entered private practice, soon limiting his work to pediatrics and becoming a Clinical Instructor at the Southern Branch of the University of California. He taught pediatrics at the Medical Department of the University of Southern California from 1912 to 1920 and was a Clinical Professor in the same subject in the College of Medical Evangelists from 1920 until 1934. He was a member of the Staff of the Los Angeles General Hospital and of the California Hospital. He was an examiner for the selective service Draft Board 1918–1919 and was president of the California Babies Hospital 1920 to 1931. He was a fellow of the American Academy of Pediatrics and a founder of the South Western Pediatric Society.

Dr. Scott was a member of many public spirited movements; he was a member of Alpha Kappa Kappa Fraternity, the University Club and was a Mason and Shriner. He belonged to numerous medical and civic organizations which are more fully listed in "Who's Who." His widow, son and daughter, in addition to his brothers and sisters and a wide medical acquaintance feel the loss of a fine man and citizen and a good physician.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Regent

SIDNEY DEAN WILGUS

Dr. Sidney Dean Wilgus, F.A.C.P., died on February 23, at his home in Rockford, Ill., at the age of sixty-eight, of coronary occlusion.

Dr. Wilgus was born in Buffalo, N. Y., February 16, 1872, and received his early education in the public schools of that city. In 1895 he received the degree of Doctor of Medicine from the University of Buffalo. From 1895 until 1902, he was Assistant Physician at St. Lawrence (N. Y.) State Hospital; he then served the next two years as Psychiatrist of Kings County and Bellevue Hospitals in New York, N. Y. In 1904 Dr. Wilgus was appointed Chairman of the New York State Board of Alienists. He served in this capacity until 1910, when he moved to Illinois to become managing officer of the Elgin State Hospital. Between 1911 and 1913 he served as managing officer of the Kankakee State Hospital. In 1913 Dr. Wilgus founded the Wilgus Sanitarium near Rockford, Ill. He was Medical Di-

rector of this institution until his death. He served as Staff Member and Lecturer in Psychiatry at the Rockford Hospital for many years, as Illinois State Alienist from August, 1929, until July, 1933, and as Professor of Psychiatry and Head of the Department of Psychiatry at Chicago Medical College since 1936.

Dr. Wilgus saw active service in both the Spanish-American War and in the World War. During the World War he served as a member of the Medical Appeal Board and performed a special hospital inspection service for the Office of the Surgeon General. In 1922 he was appointed a Major in the Medical Officers' Reserve Corps, United States Army, and in 1930 became a Lieutenant Colonel. During 1925 and 1926 he served as President of the Reserve Officers' Association of Illinois.

Dr. Wilgus was always deeply interested in the study of psychiatry. During 1927 he undertook postgraduate study in this field in Vienna. He took an active part in several psychiatric research projects of the National Committee for Mental Hygiene. One of the most important of these was a survey of conditions surrounding the care of the insane and feebleminded in four states.

Dr. Wilgus was a member of the American Psychiatric Association, the Central Neuropsychiatric Association, the Chicago Neurological Society, of which he was President during 1932, a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1930.

The death of Dr. Wilgus ends a distinguished career of one of the pioneers of psychiatry.

WILLIAM GEORGE FALCONER

Dr. William George Falconer, F.A.C.P., Clearfield, Pa., died January 3, 1940, of coronary occlusion. Dr. Falconer was born at Woodland, Pa., September 22, 1888. He attended the Perkiomen School and Pennsylvania College at Gettysburg. His medical training was received at Jefferson Medical College, from which institution he was graduated in 1919. He pursued postgraduate work at Harvard University and for many years was a member of the Medical Service and Chief of the Heart Clinic of the Clearfield Hospital. Dr. Falconer was a member of the Clearfield County Medical Society, Pennsylvania State Medical Society and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1926.

SAMUEL OSBORN

Dr. Samuel Osborn, F.A.C.P., Lansing, Mich., died December 4, 1939, at the Edward W. Sparrow Hospital of coronary thrombosis following a prostatic resection. Dr. Osborn was born at Manchester, Mich., in 1866;

received his degree of Bachelor of Science in Chemistry from the University of Michigan and his medical degree from the University of Michigan Medical School in 1903. He interned at the University of Michigan Hospital, 1903–04, and served an additional year as House Physician. Thereafter he became House Physician to the Chicago Lying-In Hospital and Dispensary, 1905. He pursued postgraduate work on two different occasions at the Massachusetts General Hospital, Boston, and also at the University of Michigan Hospital. In recent years he had retired from hospital work. He was a past president of the Ingham County Medical Society, a member of the Michigan State Medical Society and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1923.

WILLIAM GERRY MORGAN
MASTER OF THE AMERICAN COLLEGE OF PHYSICIANS

JAMES B. HERRICK
MASTER OF THE AMERICAN COLLEGE OF PHYSICIANS

PROCEEDINGS OF THE TWENTY-FOURTH ANNUAL SESSION (CONTINUED)

The Election of Masters

For the first time in eleven years the Board of Regents added to the rôle of Masters of the College by awarding this title to two eminent Fellows who have rendered distinguished service to the College:

Dr. James B. Herrick, Emeritus Professor of Medicine of Rush Medical College, holder of the Distinguished Service Medal of the American Medical Association, Ex-Regent and Ex-Vice President of the American College of Physicians.

Dr. William Gerry Morgan, Emeritus Dean and Professor of Gastro-enterology of Georgetown University School of Medicine, Regent of Georgetown University, Ex-President of the American Medical Association, Ex-Vice President, Ex-Secretary General, Ex-Governor, Ex-Regent and now Historian of the American College of Physicians.

The Annual Business Meeting

The Annual Business Meeting of the College was opened by President O. H. Perry Pepper, with the following address:

President O. H. Perry Pepper: "It is Carlyle who is always quoted as saying: 'Happy the people whose annals are blank in history books,' but he copied it from Montesquieu who probably got it from some one else. So there is no theft in my saying 'Happy is the retiring officer whose term has seen no history made.' Certainly it seems to me that the past year has seen nothing but steady healthy growth in our College. Growth in membership which now equals 4,456; growth in financial security of which you will hear from the Treasurer; growth in College usefulness with, for the first time, five research fellowships awarded; a bigger and better journal still happily under the excellent editorship of Doctor Pincoffs; with increased participation in graduate education as evidenced by successful pre-meeting courses, local gatherings of our Fellows and friendly but unentangled coöperation with other agencies toward a study of this entire problem.

"Our offspring, the American Board of Internal Medicine, is growing up a credit to both its parents, and as you heard from Doctor Irons on Monday, is now well established, financially independent and already exerting a strong and healthy influence on medicine on this continent. Our College continues to name a majority of the members of that Board, whose certification now becomes obligatory for promotion to Fellowship of Associates elected after this meeting. This is an important step which will go down in our history books and was not taken without grave debate by the Regents. I am proud that this step was made during my year as President.

"Our College Headquarters continue to prove ideal for their purposes and the cost of maintenance has been even less than our most sanguine expectations. Our Headquarters staff continues efficiently to make life easy for the President not only by telling him what he should do but by then doing all the hard work for him. Mr. Loveland scared this President out of his wits by having to undergo a serious surgical operation. I never was more interested in the recovery of anybody and I congratulate the College on the complete recovery of their Executive Secretary.

"One thing that transforms the President's task into an easy one is the wholehearted coöperation which he received from Regents and Governors. A Committee once appointed, the President knows the work will be done. I seriously doubt if the membership of the College has any idea of the amount of hard, time-consuming, self-sacrificing committee work that is done by the Governors and Regents of the College. There is a unanimity of willingness to serve which would dismay any pessimist who thinks that man is motivated only by selfishness, jealousy and laziness.

JAMES D. BRUCE
PRESIDENT (1940–41), ANN ARBOR, MICH.

O. H. PERRY PEPPER
RETIRING PRESIDENT, PHILADELPHIA, PA.

"Another thing that helps the President is the assistance he gets on all hands in the making up of the program. First in the matter of the General Chairman and local committees; this also is hard work and means sacrifice. No one refuses, every one jumps at the chance to serve. The same spirit is shown with regard to the program of the General Sessions and the Lectures. This year I wanted to emphasize our own membership in both these groups and I had fine help. It is my belief that a place on our program should be a prize to be striven for by our younger members and that it should be granted within reason in order to stimulate good work and to give training in the preparation and presentation of papers.

"Onward the College goes and it is a tremendous thing for an individual to have been permitted to march along with all the others who are doing their bit to advance the American College of Physicians."

Dr. William D. Stroud, Treasurer, presented the following report:

"The accounts of the College for 1939, have been audited by a Certified Public Accountant and scrutinized by the Committee on Finance. The year's operations indicate continued growth and a satisfactory financial situation. Through growth in Life Membership subscriptions and a transfer of approximately $30,000.00 in securities by the Board of Regents from the General Fund, the Endowment Fund on December 31, 1939, amounted to $97,499.76. The General Fund totalled $148,453.43, making the total College assets, at book value, $245,953.19. The net increase in capital, for both funds, was $23,939.07. In spite of increased activities, an appropriate credit balance was maintained. One of the former Pittsburgh depositories of the College which failed has now liquidated in full the original amount to the College, and the other two closed banks have materially reduced the balances still owing. Copies of the financial reports for 1939 will be published in an early issue of the 'Annals of Internal Medicine' for the information of all members.

"On the recommendation of the Finance Committee and the subsequent approval of the Board of Regents, the budget for 1940 has been adopted, calling for an estimated income of $105,600.00 and estimated expenditures of $80,875.00."

Mr. E. R. Loveland, Executive Secretary, presented his annual report covering all features of progress and activities in the College, dealing with membership, the publication of the Directory, handling the postgraduate courses, administering the College Headquarters, publication of financial operations, promotion of the circulation of the ANNALS OF INTERNAL MEDICINE and the general administration of the Annual Session in Cleveland.

Dr. George Morris Piersol, Secretary General, presented the following report:

"Since the last Annual Session of the College, the membership report shows that three Fellows and one Associate have been dropped for delinquency; the resignations of three Fellows and two Associates have been accepted; One Master, thirty-two Fellows and eleven Associates have been lost by death. Twenty-three Associates were dropped for failure to qualify for Fellowship within the maximum five-year period, as prescribed by the By-Laws. This year two Fellows were elected to Mastership; two hundred fifty-eight were elected to Fellowship, the majority of whom were advancements from Associateship. Only seventeen were elected directly to Fellowship because of their special qualifications and outstanding accomplishments. Two hundred ninety-two have been elected to Associateship.

"The total membership of the College is now constituted as follows:

Masters	3
Fellows	3,188
Associates	1,265
Total	4,456

"Eighteen Fellows have become Life Members since the last Annual Meeting, making a total of one hundred thirty-four names now on the Life Membership Scroll. Of the Life Members, twelve are deceased, leaving one hundred twenty-two.

"Attention should be called to the resolution of the Board of Regents passed at their regular meeting on December 17, 1939, modifying the qualifications for Fellowship. The resolution is as follows:

'RESOLVED, that after April 6, 1940, all candidates for Fellowship must present satisfactory evidence of certification by their national board for certification in their particular field, where such a board exists; this rule shall not apply to candidates from the Army, Navy and Public Health Services; it shall not apply to those who have been elected Associates prior to the above date; it may be waived in the cases of those proposed directly for Fellowship because of exceptional and outstanding qualifications.'

"In other words, regardless of their other qualifications, no Associate hereafter elected may be advanced to Fellowship who has not been certified by his or her national board of certification where such exists, except under unusual circumstances as set forth in the regulations laid down by the Board of Regents.

"It should be emphasized that the above mentioned resolution is not retroactive, and, therefore, does not apply to those who are now Associates.

"Thanks to the untiring efforts of the Committee on Postgraduate Education and the wholehearted coöperation of the Board of Governors and many of our Fellows, the intensive postgraduate courses that have preceded this Annual Session have increased in number, interest and scope. Admission to these courses has been restricted, as formerly, to members of the College and those attempting to qualify for Associateship or advancement to Fellowship. This year five were given:

Course No. 1, "General Medicine," Ann Arbor
Course No. 2, "Medicine in Industry," Detroit
Course No. 3, "Allergy," New York
Course No. 4, "Hematology," Columbus
Course No. 5, "Cardiovascular Diseases," Iowa City

"The total registration for these courses numbers 144, in spite of the fact that the registration for each course was more limited than formerly. Every course was filled, and for some courses there was a considerable waiting list. This postgraduate teaching has become one of the most important activities of the College. It is steadily gaining in popularity and justifies further development.

"Five Research Fellowships have been awarded by the College this year. These Fellowships go into effect July 1 next. They constitute another important and constructive educational activity of this organization."

At the end of his report, Dr. Piersol turned to the retiring President.

"Mr. President, in the past year, during which you have so ably and wisely guided the destiny of this College, you have become more than ever endeared to all who have had the privilege of working with you. We are deeply appreciative of the never-failing spirit of coöperation and courtesy that has marked all our associations.

"Therefore, on behalf of the Officers, Regents and Governors of the American College of Physicians, I have the honor to present you with this Gavel, an enduring symbol of the high office which you have held, as well as a token of our affection and esteem."

(Dr. Piersol presented the gavel to Dr. Pepper.)

DR. PEPPER: "Even pleasant memories tend to fade in our minds and I accept this gavel with deep satisfaction as a permanent reminder of the pleasure that I have experienced from my associations with the Regents, Governors and members of the College during my year as President."

At this point, Dr. James D. Bruce, President-Elect, was inducted as President of the College for 1940–41.

PRESIDENT BRUCE:

"MEMBERS OF THE COLLEGE: The most outstanding tendency of medicine of this generation in America is the place and opportunity given to the younger men. As a result of this, certain observable tendencies have developed of which this College and other special societies are important evidences.

"From time to time there is questioning of the requisites and standards of the various qualifying boards. In the progress of American medicine, the organization of the various special societies and the establishment of the qualifying boards rank in importance with the reorganization of the undergraduate schools about the turn of the century. In the latter, meeting the new standards entailed added burdens upon even the most favorably situated schools and a real hardship upon many, while more than half the proprietary schools were compelled to close their doors—all this quite apart from the additional hurdles for the undergraduate student. The establishment of the qualifying boards has raised new problems, comparable, at least in part, to those of a generation ago, and the means whereby the candidate may be enabled to meet the requirements now constitute a real problem for this and other similar organizations.

"The College of Physicians has assumed certain obligations which include the establishment of programs of education designed to keep our members at desirable levels of proficiency, the organization of resources to permit worthy candidates to prepare themselves for the Board of Internal Medicine and membership in the College, and the encouragement and support of research. The effective integration of all these functions justifies our use of the term *college*.

"Probably one of the reasons why misunderstanding of objectives sometimes arises is that while we may all speak fairly good English, we may not speak the same educational and professional language. In Dr. Pepper's classical dissertation on the term *internist*, he had recourse to the dictionary and while definitions therein are sometimes confusing we do get a great deal of light on the origin and meaning of words. Following Dr. Pepper's suggestion, let us turn to the dictionary to learn what it has to say about the word *college*. Here it is in part: 'pertaining to or in the nature of a college or a body of colleagues.' 'Colleague' comes from the same root as 'college.' A college then means literally 'a company or partnership of colleagues.' It may describe 'a body of persons engaged in common pursuits or having common duties and interests and sometimes, by charter, peculiar rights and privileges,' or 'a company of scholars or friends of learning incorporated for study and instruction in the higher branches of knowledge, usually of a professional kind.' The main point is that a college is an institution or organization where there is a body of self-governing associates or equals bound together in the pursuit of their common interests and having certain powers and privileges conferred on them or delegated to them.

"It would seem then with the establishment of the Board of Internal Medicine, a qualifying agency, that the College with programs such as these in which the various phases of medical advances are reviewed and brought up to date, with a program of postgraduate education so well received by our members and those desirous of membership, together with the encouragement and support given to scientific research, is filling the function of and entitled to the honored designation of *college*.

"As I review the qualifications required by the Board of Internal Medicine and the College, it leaves me with but one major concern, and that is the seeming impossibility of the attainment of college affiliation by a not inconsiderable group of younger internists; not, indeed, through the stringency of the requirements of the Board but through the fact that we have in this country at the present time too limited opportunities to provide requisite disciplines and experiences for prospective candidates for membership. Thus I was particularly pleased with the commission from Dr. Pepper to attend a meeting with Dr. Hugh J. Morgan, chairman of our Postgraduate Committee; Dr. Ernest E. Irons, chairman of the Board of Internal

Medicine, and Dr. W. D. Cutter, secretary of the Council of the American Medical Association, for a discussion of the mutual interests and responsibilities of the educational and qualifying phases of these collaborating agencies. Here I was gratified to find complete awareness of the urgent importance of the problems and a determination to give a maximum flexibility to the requirements of the Board, without any thought of a lowering of standards.

"Were I to select that which in my opinion is the most important task for the College during the coming year, it would be the assembling and utilizing of all our present educational resources and adding, as rapidly as may safely be done, new methods whereby candidates may qualify, having in mind at all times the objectives of the College and the standards set up by the Board.

"I would take the system we know, suggesting how it might be strengthened where it is weak, repaired where it has crumbled, and rebuilt where new needs require additions to its fabric. . . . While social, economic and other humanistic factors are a part of the fabric, the basic thought in all these considerations must be toward the advancement of science and its utilization for human needs. No body of medical men has this goal more clearly in mind than the American College of Physicians.

"I am not unmindful of the great honor you have conferred upon me. For this I thank you. Also, I am not unmindful of the responsibilities of this high office. May I express the hope that any lack in professional preparedness or administrative ability will be, at least in part, compensated for by the devotion and humility with which I approach the task."

President Bruce called upon Dr. Sydney R. Miller, Chairman of the Committee on Nominations, to present the nominations for the elective offices, for the Board of Regents and for the Board of Governors, according to the terms of expiration for the current year.

Dr. Sydney R. Miller: "Mr. President, the Nominating Committee, composed of Dr. William J. Kerr, Dr. James J. Waring, Dr. Charles E. Watts, Dr. Clarence L. Andrews, and myself, nominate the following for office:

"(*A*) *For the Elective Offices:*

President-Elect .....Roger I. Lee, Boston, Mass.
First Vice President .....Robert A. Cooke, New York, N. Y.
Second Vice President .....James G. Carr, Chicago, Ill.
Third Vice President .....Henry M. Thomas, Jr., Baltimore, Md.

This list of nominees has been duly published in the 'Annals of Internal Medicine' at least one month before the present date."

There were no nominations from the floor and on motion, seconded and duly carried, nominations were closed and the Secretary General was instructed to cast the ballot for the above nominees.

Dr. Miller:

"(*B*) *For the Board of Regents:*

Term Expiring 1941

T. Homer Coffen, Portland, Oregon

Term Expiring 1943

David P. Barr, St. Louis, Mo.
J. Morrison Hutcheson, Richmond, Va.
Walter W. Palmer, New York, N. Y.
O. H. Perry Pepper, Philadelphia, Pa.
Gerald B. Webb, Colorado Springs, Colo."

There were no nominations from the floor and on motion duly seconded and carried, nominations were closed and the Secretary General was instructed to cast the ballot for the election of the above nominees to the Board of Regents.

DR. MILLER:

"*(C) For the Board of Governors:*

Term Expiring 1943

Fred W. Wilkerson, Montgomery .....ALABAMA
Fred G. Holmes, Phoenix .....ARIZONA
Lewis B. Flinn, Wilmington .....DELAWARE
Turner Z. Cason, Jacksonville .....FLORIDA
Glenville Giddings, Atlanta .....GEORGIA
LeRoy H. Sloan, Chicago .....ILLINOIS (Northern)
C. W. Dowden, Louisville .....KENTUCKY
Eugene H. Drake, Portland .....MAINE
Louis Krause, Baltimore .....MARYLAND
John G. Archer, Greenville .....MISSISSIPPI
Ernest D. Hitchcock, Great Falls .....MONTANA
LeRoy S. Peters, Albuquerque .....NEW MEXICO
Charles F. Tenney, New York .....NEW YORK (Eastern)
A. B. Brower, Dayton .....OHIO
Homer P. Rush, Portland .....OREGON
M. D. Levy, Houston .....TEXAS
Elmer L. Sevringhaus, Madison .....WISCONSIN
Ramon M. Suarez, San Juan .....PUERTO RICO
George F. Strong, Vancouver .....ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN"

There were no nominations from the floor and on motion duly seconded and carried, nominations were closed and the Secretary General was instructed to cast the ballot for the election of the above Governors.

President Bruce requested Dr. D. Sclater Lewis and Dr. John H. Musser to escort the new President-Elect, Dr. Roger I. Lee, to the rostrum.

President Bruce introduced Dr. Lee amid wide applause.

The following resolution, moved by Dr. Charles F. Tenney and seconded by Dr. Hugh Morgan, and unanimously carried, was spread upon the Minutes:

"RESOLVED, that the cordial thanks of the American College of Physicians be extended to the Retiring President, Dr. O. H. Perry Pepper; to the General Chairman, Dr. Howard T. Karsner; to the chairman and members of his various committees, individually and collectively, to the Cleveland Academy of Medicine, for their faithful work in the preparation and conduct of the Cleveland Session; to the Ladies Entertainment Committee for its efficiency, hospitality and courteous entertainment of our ladies; to the Western Reserve University and the hospitals and institutions of Cleveland for putting their facilities at the disposal of the College, and for their helpful participation; to the public press; to the Cleveland Convention and Visitors' Bureau and its officers for their assistance; to the Cleveland Public Auditorium and its staff for coöperation and help; to the Hotel Statler for its assistance and aid in providing for our entertainment and comfort."

American College of Physicians, Inc.

Balance Sheet, December 31, 1939

General Fund

Assets			*Liabilities*	
Current:			*Current:*	
Cash in banks and on hand		$ 11,361.33	Deferred Income:	
Accounts Receivable:			Advance Subscriptions, Annals of Internal Medicine	$ 12,617.18
Advertising	$ 923.19		24th Annual Session, Exhibit	2,481.45
Hornblower and Weeks	4,341.11	5,264.30		
Inventory of Keys, Pledges and Frames, at cost		342.70	Total Current Liabilities	$ 15,098.63
Accrued Income on General Fund Investments		218.02		
Accrued Income on Endowment Fund Investments, Due to General Fund		705.30		
Investments at Book Value		78,526.36		
Insurance Deposit		555.00		
Total Current Assets		$ 96,973.01		
Deferred:				
Expenses, 24th Annual Session		3,060.86		
Claims:				
Banks in process of liquidation:				
Exchange National Bank, Pittsburgh	$ 1,166.14			
Highland National Bank, Pittsburgh	2,499.86	3,666.00	General Fund, as annexed	$148,453.43
Fixed:				
College Headquarters, Real Estate	$57,728.45			
Less, Allowance for Depreciation	3,000.00	54,728.45		
Furniture and Equipment, at cost	$10,155.39			
Less, Allowance for Depreciation	5,031.65	5,123.74		
		$163,552.06		$163,552.06

Endowment Fund

Cash in banks	$ 7,955.26	Endowment Fund, Principal	$ 97,499.76
Accrued Interest	705.30	Accrued Income, Due to General Fund	705.30
Investments at Book Value	89,544.50		
	$ 98,205.06		$ 98,205.06
Total Assets	$261,757.12	Total Liabilities and Funds	$261,757.12

General Fund

For the Year Ended December 31, 1939

Balance, January 1, 1939			$153,449.87
Less:			
Transfer to Endowment Fund of the Initiation Fees of Life Members		$ 970.00	
Transfer to Endowment Fund per resolution of Board of Regents, December 17, 1939		29,811.03	30,781.03
			$122,668.84
Summary of Operations for the Year ended December 31, 1939:			
Income:			
Annual Dues		$27,597.89	
Initiation Fees		15,506.00	
Subscriptions, Annals of Internal Medicine		29,930.31	
Advertising, Annals of Internal Medicine		9,198.90	
Income from Invested Funds, General		4,683.49	
Income from Invested Funds, Endowment		2,674.33	
Exhibits, 23rd Annual Session		11,671.44	
Guest Fees, 23rd Annual Session		530.00	
Banquet, net, 23rd Annual Session		298.61	
Profit on Keys, Pledges and Frames		196.45	
Dividend on Perpetual Insurance Deposit		60.00	
Profit on Equipment Sold		7.50	
Sale of Directory, 1937		4.95	
Total Income			$102,359.87
Expenses:			
Salaries		$23,843.45	
Postage, Telephone and Telegraph		3,763.12	
Office Supplies and Stationery		1,199.15	
Printing		22,257.42	
Traveling Expenses		6,390.22	
College Headquarters:			
Maintenance	$1,581.38		
Heat, Light, Gas and Water	612.90		
Taxes	1,176.22		
Insurance	82.16	3,452.66	
Loss on Sale of Investments, General Fund		1,200.71	
Depreciation on Building, Furniture and Equipment		1,758.96	
Grant to Commission on Graduate Medical Education		100.00	
1939 Directory, net		2,524.84	
Postgraduate Courses, net		481.43	
John Phillips Memorial Prize		41.75	
Research Fellowships		2,713.50	
Other Expenses:			
23rd Annual Session	$4,813.55		
Annals of Internal Medicine	470.46		
Miscellaneous	1,564.06	6,848.07	
Total Expenses			$76,575.28
Net Income for the Year Ended December 31, 1939			$ 25,784.59
Balance, December 31, 1939			$148,453.43

Endowment Fund

For the Year Ended December 31, 1939

Principal Account, January 1, 1939			$ 68,564.25
Add:			
Life Membership Fees received during 1939		$ 2,350.00	
Transfer of Initiation Fees of New Life Members from General Fund		970.00	
Transfer from General Fund, per resolution of Board of Regents, December 17, 1939		29,811.03	33,131.03
			$101,695.28

Deduct:		
Loss on Sale of Investments		4,195.52
Principal Account, December 31, 1939		$ 97,499.76
Income Account:		
Income from Investments earned during 1939		$ 2,674.33
Deduct:		
Research Fellowships	$ 2,713.50	
John Phillips Memorial Prize	41.75	2,755.25
Excess of Expenses over Income, charged to General Fund Operations for 1939		$ 80.92

INVESTMENTS

December 31, 1939

Par Value	*Bonds*	*Endowment Fund Investments*	*General Fund Investments*	
$ 3,000	Appalachian Electric Power Co., Deb., 4½s, 1948	$ 3,105.00		
5,000	Carolina Clinchfield & Ohio Ry., 1st & Consol. Mort., Series "A," 6s, 1952	5,413.40		
5,000	Florida Power Corp., 1st Mort., Series "C," 4s, 1966	4,485.90		
5,000	Great Northern Ry., Gen. Mort., Series "B," 5½s, 1952	4,463.45		
5,000	Michigan Consolidated Gas, 1st Mort., 4s, 1963	5,130.95		
5,000	North American Co., Deb., 3½s, 1949	5,219.52		
5,000	Northern States Power Co., 1st & Ref. Mort., 3½s, 1967	4,806.25		
5,000	Ohio Edison Co., 1st Mort., 4s, 1965	5,287.50		
4,000	Ohio Public Service, 1st Mort., 4s, 1962	4,240.75		
5,000	Pennsylvania RR, Gen., 4¼s, Series "E," 1984	5,013.10		
2,000	Port of New York Authority, Interstate Tunnel, Series "E," 4¼s, 1958	2,065.40		
2,000	U. S. Treasury, 4s, 1944/54	1,998.13		
20,000	U. S. Treasury, 3¼s, 1945	19,887.50		
5,000	Virginia Public Service, 1st & Ref., 5½s, 1946	5,133.65		
$76,000	TOTAL, Bonds	$76,250.50		
Shares	*Stocks*			
50	American Brake Shoe & Foundry Co., Conv., Pfd.		$ 6,163.60	
50	American Gas & Electric Co., $6.00, Pfd.		5,537.25	
50	Atchison, Topeka & Santa Fe, 5%, Pfd.		4,970.75	
20	Central New York Power Corp., 5s, Pfd.		1,944.45	
100	Chase National Bank of New York		4,550.00	
100	Commercial Investment Trust Corp., Common		5,143.25	
50	Continental Can Co., $4.50, Cum. Pfd.	5,125.00		
100	Curtiss-Wright Corp., Class A		2,652.80	
50	E. I. du Pont, 6%, Cum., Deb.		6,899.00	
25	Eastman Kodak Co., Common		4,200.38	
75	General Motors Corp., Common		3,594.53	
40	Great Atlantic & Pacific Tea Co., 7%, 1st, Pfd.		5,133.75	
20	Gulf States Utilities, $6.00, Cum. Pfd.		2,245.30	
50	International Harvester, 7%, Pfd.	8,169.00		
50	International Nickel Co. of Canada, Ltd., Common		2,432.10	
20	J. C. Penney Co.		1,375.30	
50	Johns-Manville Corp., Pfd.		6,326.10	
40	Monsanto Chemical Co., $4.50, Cum. Pfd., A		4,715.30	
50	Montgomery Ward & Co., Inc., Common		2,594.75	
150	Pacific Gas & Electric Co., 6%, Pfd.		4,640.50	
50	Timken Roller Bearing Co.		3,407.25	
	TOTAL, Stocks	$13,294.00	$78,526.36	
	TOTAL, Investments	$89,544.50	$78,526.36	$168,070.86

ANNALS OF INTERNAL MEDICINE

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Manuscripts. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006–2008.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

Reprints. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

Reviews. The Annals will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

Subscription. This periodical is issued monthly, new volumes beginning with the July number each year. Subscriptions may be by the volume or year, but the volume basis is especially recommended. Volumes will consist of approximately 2,000 pages. Subscription price per volume, or per annum, net postpaid: $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $7.50, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.00. Members of the American College of Physicians receive the Annals of Internal Medicine in connection with the payment of annual membership dues, of which seven dollars is for a year's subscription to the publication. Checks should be drawn to the order of W. D. Stroud, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

Business Correspondence. All correspondence relating to business matters, advertising, subscriptions to the Annals, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Publication Office or to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

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